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CASES OF OCCUPATIONAL ASTHMA ASSESSED AT THE NATIONAL INSTITUTE FOR OCCUPATIONAL HEALTH - OCCUPATIONAL MEDICINE CLINIC FROM 1997 TO 2007

Candidate

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Thesis statement

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Occupational Medicine

Johannesburg 2010

Supervisors:

Prof David Rees

Dr Danuta Kielkowski

DECLARATION

I, Spoponki Mamohapi Alina Kgalamono declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Occupational Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or other University.

_____

Spoponki Mamohapi Alina Kgalamono

_____ day of _____2010

DEDICATION

My gratitude goes to God almighty for bringing me this far. This report is dedicated to my husband, our lovely children Lerato, Thato and Thapelo for their patience and undying support. To my mom for her encouragement.

In memory of my loving father

Isaac Mojela Vena

1931-1984

PRESENTATIONS ARISING FROM THIS STUDY

The preliminary results of this study were presented at the National Institute for Occupational Health Research Day that took place in Johannesburg in 2008.

ABSTRACT

Title

Cases of occupational asthma assessed at the National Institute for Occupational Health Occupational Medicine Clinic from 1997 to 2007.

Background

Occupational asthma is one of the most commonly reported occupational respiratory diseases in industrialized countries. Literature suggests that about 15% of all adult-onset asthma is caused by workplace exposures. It is potentially preventable and the prognosis is good with early diagnosis and adequate treatment. However, occupational asthma is under-diagnosed and under-reported. Identification of common causative agents and employment of preventative measures are necessary for proper management and control.

Objectives

1. To characterize occupational asthma cases assessed at NIOH Occupational Medicine Clinic from 1st January 1997 to 31st December 2007 in terms of:
    - types of industries, occupations and agents
    - duration of exposure prior to onset of occupational asthma
    - time from onset of symptoms to diagnosis
    - nature of exposure e.g. intermittent, daily, etc.
2. To investigate factors influencing latency period in cases of sensitizer-induced asthma
3. To investigate factors influencing lag time to diagnosis in cases of sensitizer-induced asthma

Methods

A record review of a series of cases of occupational asthma was done. All cases of occupational asthma diagnosed from 1st January 1997 to 31st December 2007 by NIOH doctors were identified from the Clinic's electronic database. All the records of patients who had a final diagnosis of occupational asthma were assessed using a standard data capture sheet. Doubtful cases were presented at the NIOH Occupational Medicine clinical discussion meeting for a consensus decision as to whether they qualified to be included in the study or not. Ethical approval was granted by the University of the Witwatersrand Human Research Ethics Committee (Medical).

Results

One hundred and forty two cases of occupational asthma were identified. Of these, 131 were sensitizer-induced and 11 were irritant-induced asthma. Low molecular-weight agents were in the majority with isocyanates, welding fumes, vanadium being the most common. Within the high molecular weight category, wheat was the most common. The majority of cases emanated from the Engineering, Chemical, Smelter and Food industries. Latency period from first exposure to development of symptoms was surprisingly long: a mean of 9.8 years and a median of seven years. The time from onset of symptoms to diagnosis was also long (mean of 4.9 years and median of three years). Younger cases had a shorter latency period and a longer delay in diagnosis. Agents and jobs for irritant-induced asthma cases varied widely and some came from unexpected industries.

Discussion

This review of asthma referrals to the NIOH Occupational Medicine Clinic has highlighted causative industries and identified exposure agents implicated in cases of occupational asthma. The very wide range of industries, occupations and agents associated with these cases is suggestive of a wide-spread occupational asthma problem in the region referring cases to the Clinic. The long latency period and delay in diagnosis are of concern since prompt diagnosis and removal from exposure is associated with a better prognosis. Irritant-induced asthma is infrequently reported in the local literature, but the range of agents and jobs is possibly indicative of under-diagnosis.

Conclusion

Occupational asthma is potentially preventable. New cases still arise particularly in poorly controlled workplaces which are capable of employing basic measures to control exposures. Medical surveillance, prompt diagnosis, proper medical management and application of workplace preventative measures are essential in decreasing the burden of disease and impairment.

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CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

In this chapter, work-related asthma is defined. A distinction is made between the types of occupational asthma. The public health importance of occupational asthma and the socioeconomic consequences for workers diagnosed with the disease are highlighted. Briefly, the National Institute for Occupational Health (NIOH) Occupational Medicine Clinic – the Clinic which is the source of study subjects, is described. Common industries, occupations and agents responsible for the majority of cases of occupational asthma are described based on literature from population studies, surveillance programmes and case series published globally and locally. A brief overview of studies of occupational asthma prognosis (health outcomes) is done and the chapter ends with the aims and objectives of this study.

Asthma caused by work (occupational asthma) is the most commonly reported occupational respiratory disease in industrialized countries and it is fast approaching pneumoconiosis in developing countries.[1] Several studies looking at the proportion of adult-onset asthma cases attributable to work exposures indicate that about 15% of all adult-onset asthma is caused by workplace exposures.[2-6]

This growing recognition of the importance of occupational asthma warrants exploration of preventive strategies. Primary prevention requires the identification of occupational exposures in terms of agents, jobs and industries associated with such exposures, so that interventions to control exposure can be prioritized. Such strategies have had some success in high-income countries.[7] One means of identifying the common causes of occupational asthma is to review the exposure histories of cases presenting to referral clinics.

Additionally, in developing countries, there is incomplete knowledge of asthma -causing agents particularly as the number of new agents introduced in many workplaces increases. There is a possibility of new causes of occupational asthma emerging from unstudied workplaces; justifying identification of agents in a group of workers from different industries. Therefore, a case series study of patients from a variety of industries provides the opportunity to identify such settings for preventive strategies.

1.1 BACKGROUND

1.1.1 Work-related asthma and occupational asthma

Work-related asthma is a broad term that includes asthma caused by workplace exposures (that is, occupational asthma) as well as pre-existing asthma made worse by work exposures (work-exacerbated asthma).[8] Two types of occupational asthma are distinguished by whether they appear after a latency period. Sensitizer-induced asthma appears after a latency period of exposure necessary for the worker to acquire sensitization to the causal agent. This type includes occupational asthma that is induced by an IgE mechanism (most high- and some low-molecular-weight agents), and occupational asthma in which an IgE mechanism has not been demonstrated consistently (low-molecular-weight agents, such as diisocyanates, western red cedar and acrylates). On the other hand, irritant- induced asthma is characterized by the absence of a latency period. It occurs after accidental exposure to high concentrations of a workplace irritant and symptoms occur within 24 hours following exposure. This clinical entity used to be known as Reactive Airway Dysfunction Syndrome (RADS). The pathophysiologic mechanism underlying irritant-induced asthma is not well understood, and it is not known why the asthmatic response persists in certain individuals.[9-12]

Controversy still exists about whether intermittent moderate-level exposure and chronic low-level exposure to irritants can cause irritant-induced asthma. Both possibilities are legitimate.[13, 14] However, because there is no consensus yet, only the typical irritant induced asthma from one-time high exposure to an irritant (RADS) has been considered in this study.

1.1.2 Burden of occupational asthma in South Africa

South Africa does not have a surveillance scheme or register for recording occupational diseases; as such the incidence and prevalence of occupational asthma in South Africa is not known. A few studies done in different workplaces have reported estimated prevalences and incidences although comparison among them is difficult because of different definitions of asthma and diagnostic methods used.[1]

In the same paper, the authors presented a table of South African studies with prevalence ranging from 3% in wood working operations to a high cumulative incidence of 41% in platinum refinery workers. Those studies that reported a low prevalence[15] attributed it to under-recognition and lack of occupational health surveillance programmes in small

workplaces. The Surveillance of Work-related and Occupational Respiratory Diseases in South Africa (SORDSA) programme 1999 report identified occupational asthma as the second most common occupational respiratory disease in South Africa after pneumoconiosis.[16] Since the collapse of SORDSA, there is no nationwide data available to describe the distribution or causes of work-related respiratory diseases in South Africa; as such, targeting intervention is a challenge. However, statistics from the NIOH Occupational Medicine Referral Clinic's annual report, [17] shows occupational asthma as the most frequently assessed occupational disease in the Clinic. This information, although not nationally representative, provides an opportunity to describe cases of occupational asthma assessed at this Clinic.

1.1.3 Socioeconomic impact of occupational asthma

Occupational asthma often affects young and economically active patients. This chronic condition is a cause of morbidity and affects quality of life and future employment, and may lead to loss of income.[18]

Avoidance of exposure to the causative agent is one part of management of sensitizer induced asthma that has shown to significantly improve symptoms and offers the best chance for recovery. However, in many instances, control of workplace exposures is not possible and workers have to be relocated or resign, with uncertain prospects of future employment. This is particularly true of many small workplaces without alternative areas free of exposure to the causal agent or other triggers. The result is job and income loss for affected workers.

Studies that have investigated the socioeconomic impact of occupational asthma have consistently found deterioration in the socio economic status of a high proportion of patients; be it through job loss, demotion, limitations in doing daily activities or frequent absenteeism from work. The study by Ameille et al. recorded an average decline in income of more than 50% in those people who were removed from their jobs as opposed to about 20% income loss in those who remained in their current employment.[18-23]

Although compensation under South African legislation covers medical costs, including visits to general practitioners and hospitalization, the monetary compensation does not match previous income (Compensation for Occupational Injuries and Diseases Act No. 130 of 1993). At times patients suffer financial losses while waiting for compensation outcome, which can take more than a year. The situation in South Africa (as opposed to many developed countries) is further complicated by failure of the compensation system to compensate for loss of income and retraining for other jobs within or outside the company. A high unemployment rate with many workers being unskilled labourers with limited formal education adds to the socio-economic

burden. It is not uncommon to find some workers opting to remain in exposed jobs for financial reasons. This however, leads to deterioration in health.[24] Compensation systems that aim at retraining, rehabilitation and relocation rather than paying for impairment might be effective in positively changing the socioeconomic outcomes of occupational asthma.[25]

1.1.4 Primary prevention and prognosis

Unlike most other forms of asthma, occupational asthma is potentially preventable by controlling workplace exposures.[26] One Canadian study[3] concluded that the removal of exposure to known inducers could prevent as much as 18% of adult-onset asthma in that country. Another study, by Ameille et al.,[27] showed that early removal from exposure is important for treatment and preventing persistent disease. Reducing or eliminating exposure to the offending agent will usually reduce the severity of symptoms or, in some cases of early intervention, it may eliminate symptoms completely. Persons who remain exposed are more likely to have persistent and troublesome asthma.

The most important aspect of the definition of occupational asthma is evidence of a direct causal relationship between workplace exposures and development of asthma. [28] Knowledge and understanding of these asthma-causing agents is important for primary prevention of occupational asthma through exposure control. Several studies [29-31] have outlined ways to prevent the occurrence of occupational asthma by controlling the exposures because the risk of developing occupational asthma is determined less by individual susceptibility (atopy, smoking, HLA phenotype) and more by the level of exposure to its causes. In general, the higher the exposure, the greater the risk and by implication, lowering the level of exposure reduces the incidence of disease.[30]

There are over 300 agents known to cause occupational asthma.[32, 33] It is important to identify these agents as management and outcome may differ depending on the type of agent a worker is exposed to. For example, exposure to a sensitizer generally warrants complete removal from exposure whereas reducing workplace exposure to respiratory irritants and environmental allergens; limiting exposure to non-occupational irritants such as tobacco smoke; optimizing anti-asthma therapy, educating the patient on the usage of the drugs, and emphasizing the importance of compliance often allow workers with irritant induced asthma to continue working in the same job. However, these measures are not sufficient to prevent the relapse of sensitizer induced asthma as even minute amounts can evoke a reaction severe enough to cause major clinical consequences. Although one of the challenges in prevention is the fact that

there are several hundred known agents arising from many occupations in most major industries, identification and control of such agents is still possible.[34]

Companies without established medical services lack capacity to identify agents and conduct medical surveillance which leads to delay in the diagnosis of occupational asthma. Patients diagnosed late, do poorly as their disease is more severe at the time of diagnosis; hence the importance of early diagnosis and early removal from the offending agent.

From a public health point of view, it is important to identify industries, jobs and agents causing occupational asthma because this can lead to targeted intervention. In industries where there is a known risk to workers, steps can be taken to eliminate or at least reduce the number of workers who will be affected.

1.1.5 The NIOH Clinic

The NIOH has run a referral Occupational Medicine Clinic since 1972.[35] The Clinic receives referrals from within South Africa (particularly Gauteng and Mpumalanga) and neighbouring. Kwa-Zulu Natal, Western Cape and Free State provinces run similar occupational medicine clinics but on a smaller scale, hence only complicated cases from these provinces are referred to NIOH. Patients are referred by a select group of medical practitioners and nurses seeking confirmation of the diagnosis or assistance with submission of compensation claims. Cases referred here are either asthma cases for confirmation of occupational asthma or as probable asthma for further diagnostic work up at the Clinic. Cases come from a variety of industries but there are industries important in occupational asthma that are not within the vicinity of the NIOH e.g., platinum refining. As such, cases from these industries rarely present to the NIOH Clinic.

The majority of the patients referred to the clinic suffer from occupational lung diseases. These include, but are not limited to, pneumoconioses, occupational asthma, tuberculosis, chronic obstructive pulmonary disease (COPD) and occupational lung cancers. Each year on average the Clinic assesses approximately 220 cases and about 20% are occupational asthma cases. For many years, occupational asthma was the second most common occupational lung disease assessed in the Clinic. But in the past two years, occupational asthma has become the most commonly assessed lung disorder.[36]

The NIOH Clinic, because it assesses cases in and around Gauteng, is an important source of occupational asthma cases and therefore can provide a means of identifying industries, jobs and agents in the catchment area for targeted prevention.

1.2 LITERATURE REVIEW

1.2.1 Industries, jobs and agents in occupational asthma

There are over 300 agents known to cause occupational asthma.[32, 33] Exposure agents can be categorized crudely into high molecular weight (HMW) and low molecular weight (LMW). The high-molecular-weight compounds are typically animal and plant derived proteins or polysaccharides such as wheat flour and animal dander that cause an IgE-dependent immune response. The low-molecular-weight compounds include organic and inorganic compounds that, with a few exceptions, are not associated with an IgE mechanism, but are chemicals that can also initiate an immune response after repeated inhalation. These agents can cause sensitization through a hapten-mediated effect. The nature of the immune response is more complex for the low-molecular-weight chemicals than it is for the high-molecular-weight agents.

1.2.1.1 Global causes of occupational asthma: international studies

A: ***Population studies***

Although results from population studies are valid for the specified population, there are some similarities across populations particularly in industries with similar jobs and exposures allowing for comparisons. The strength of population-based studies is the inclusion of occupational asthma workers who have left the workplace rather than only those who are currently exposed, thus giving a more complete picture and reducing the healthy-worker effect.[30] They will, however, be influenced by the nature of industries dominant in the regions of the surveyed populations.

There is a lack of general population-based epidemiological studies assessing agents related to work- related asthma.[37] The few that have examined the relationship between occupational exposures and asthma have managed to report generally about exposures and not specific chemicals or dust types.[38-40]

The majority of population studies have reported on the risk of asthma in different occupational groups. These studies do not lend themselves to comparison because methodologies and case definitions are not similar across studies. Some studies defined asthma based on evidence of bronchial hyper responsiveness, while others collected information on subjective account of asthma symptoms and medication used. Therefore, there is a possibility of misclassification of adult onset asthma as occupational asthma hence such studies need to be followed up by epidemiological studies of assessment of exposures and elevated risks in these occupational groups and industries. Results from some population studies looking at risk of developing asthma in certain occupational groups are presented below. The risk varies depending on the geographical location and dominant industries in that population or community.

In Singapore, the risk was elevated for service workers, cleaners, textile workers, garment makers, electronic production workers, printers, construction or renovation workers and manufacturing related workers.[41]

In Spain, the highest risk of asthma in those between 20-44 years of age was observed for laboratory technicians, spray painters, bakers, plastics and rubber workers, welders and cleaners.[42]

A New Zealand study identified certain occupations significantly associated with asthmatic symptoms and bronchial hyper responsiveness in New Zealand adults aged 20-44 years. The highest risk occupations were farmers and farm workers, laboratory technicians, food processors (other than bakers), chemical workers and plastic and rubber workers. It is surprising that some groups known to be associated with occupational asthma, like bakers and spray painters, did not show excess risk in Singapore and New Zealand. The reasons are not clear but could be attributed to low numbers in the groups or improved standards of work, thus truly reflecting low prevalence.[43]

A Northern California study that evaluated the role of occupational factors on the prevalence of self-reported asthma, chronic bronchitis and asthma-like symptoms among women more than 54 years of age found high risk in artists, writers, decorators, photographers, social workers and homemakers. It must be noted that this is a specific group (women only) and occupational exposures were arbitrarily measured by taking only the last job and the longest occupation in which a subject was employed. Thus, information on other jobs that may have had exposures that could cause asthma was lacking. Common industry in this community is farming (grapes). Farm workers as a group did not show a high risk as would have been expected. The reason for

this might be the low numbers of women in this industry or less intense exposures in women than in men.[44]

In Europe and other industrialized countries, authors found high risk in farmers, painters, plastic workers, cleaners, spray painters and agricultural workers. The study used a strict definition of asthma that included metacholine challenge test, questionnaire on symptoms and asthma medication.[45]

A South Finland population study assessing relationship between occupation and risk of developing asthma in adults found an increased risk both in traditional industries and several other non-industrial occupations. For men, the risk was increased in bakers, food processors, textile workers, painters, construction workers, electrical and electronics production workers, laboratory technicians, storage workers, laundry workers, shoemakers and repairers, metal plating and coating workers. For women, shoemakers, jewelry engravers, waitresses, cleaners, dental workers, molders and bakers were at a high risk of asthma.[46]

A US population study of the prevalence of asthma by industry reported higher risk in those employed in printing, publishing and allied industries for white males. For white females, prevalence was elevated in the health care industry. For blacks, prevalence was higher in furniture, lumber, wood and entertainment industries. Other industries of importance were automobile dealers and gasoline station, durable goods, personal services and sanitary services.[47] This study showed that asthma prevalence patterns differed by race and sex.

These population studies identified occupational groups and industries associated with high risk of development of asthma. This can form the basis for targeted prevention of occupational asthma. The advantage of community based studies is that individuals are selected irrespective of their current job and the degree of selection bias may be significantly reduced. However, methodological challenges are common.

B: Surveillance programmes

Surveillance programmes which rely on specialist physician notification of occupational respiratory diseases have been established in some countries because of limitations in many sources of occupational diseases data, such as workers' compensation data.[48] The majority of these schemes are similar in voluntary reporting methods with a few differences in the categories of health care workers reporting to the scheme. Although these programmes rely on voluntary reporting of cases which leads to underestimation of incidence and prevalence, and

also the unbalanced specialists' coverage within the same country which indicates variable accessibility, they still offer valuable incidence and causation statistics for occupational respiratory diseases.[49] One such example is the Surveillance of Work-related and Occupational Respiratory diseases (SWORD) programme in the United Kingdom, which has been running for more than a decade. Data from SWORD has helped identify new agents causing occupational asthma and led to these agents being further investigated and controlled.[50]

The highest incidence rate of occupational asthma was reported in the manufacture of wood products and latex. Asthma due to latex was seen in specific groups like laboratory workers, shoe workers and healthcare workers.[51]

The SHIELD (not an acronym) scheme was started in 1989. It is a reporting scheme which only studies the general and occupation specific incidence of occupational asthma in the West Midlands area of England.[48] A publication on the first three years' results by Gannon et al. reported the common agents to be isocyanates, flour and colophony; and the most common occupation was spray painters.[52]

A study by di Stefano et al.[53] aiming at estimating the incidence of occupational asthma in the West Midlands in 1990-97, found spray painters to be the highest risk occupation, followed by electroplaters, rubber and plastic workers, bakery workers and moulders. Isocyanates remained the most common causative agent. There was a decrease in reported cases due to colophony, flour and wheat. Increasing numbers of latex and gluteraldehyde were also noted. A recent publication reported on the 15 years (from 1989 to 2004) of SHIELD noted a decline in the number of cases of occupational asthma exposed to latex and gluteraldehyde. This was attributed to better control of exposures. Colophony was also declining but there were outbreaks due to metals like cobalt and chrome.[54]

The French Observatoire National des Asthmes Professionnels (ONAP) programme, was set up to develop a monitoring system for occupational asthma in France and to promote primary prevention based on a better knowledge of the incidence of occupational asthma and its causal agents. It is a voluntary reporting system by physicians, mainly occupational and chest physicians. The highest incidence rates of occupational asthma in France were observed in bakers and pastry makers, hairdressers, car painters and wood workers. The most frequently identified agents were flour, isocyanates, latex, aldehyde, persulphate salts and wood dusts.[55]

In the USA, the Sentinel Event Notification System for Occupational Risks (SENSOR) has been operating in six states since 1988. The objectives of SENSOR are to identify potentially dangerous sentinel cases in the work environment and to subsequently initiate investigations and implement interventions. Cases reported must be diagnosed by a physician. The most common agents reported in the 1999 report were metal working fluids, cleaning agents and isocyanates. Industries where cases of work-related asthma were identified were manufacturing (includes food, primary metal, chemical, transport equipment, plastic and rubber products manufacturers) and health care and social services.[56] This could be attributed to under-reporting or more likely to the success of prevention strategies in various workplaces.

In Canada, the first reported programme was from a British Columbia group[57] which evaluated the feasibility of a surveillance program for occupational respiratory disease based on voluntary reporting by physicians. The methods used were similar to the UK's SWORD project. The specialists involved were both respiratory and occupational physicians. In 1991, they reported on the first year's RESULTS. The most common agent thought responsible for occupational asthma was plicatic acid from Western Red Cedar, followed by chemicals and isocyanates. The higher incidence of Western Red Cedar asthma than that found in other parts of the world was thought to be due to the large forest industry in British Columbia. The programme did not continue past the pilot stage due to lack of funding.[48]

The PROPULSE (PROjet PULmonaire SEntinelle) scheme in Quebec[58] was also based on the UK's SWORD model with similar reporting procedures and the same diagnostic categories, but different participating physicians comprising allergists and respiratory physicians, but no occupational physicians. Isocyanates and flour were the most commonly reported agents. Although providing useful data, this programme also did not progress past the pilot stage due to lack of funding.[48]

The New Zealand Notifiable Occupational Disease System (NODS) was established in March 1992. It is a voluntary system whereby occupational physician specialists, general practitioners, occupational health nurses, health professionals and individuals can notify a health-related condition suspected to have risen from work. The numbers reported were small because many practitioners and specialist are unaware of the scheme. However, recognized asthma causing agents like isocyanates, remained the most common agents.[59]

In Australia, a scheme known as SABRE (Surveillance of Australian Workplace-Based Respiratory Events) was established in 1997. It is based on voluntary reporting by physicians.

Publication of results from the first 3.5 years reported wood dust as the most common agent, followed by isocyanates. The incidence of asthma was lower compared to surveillance schemes in other countries. The authors attribute this to under-ascertainment of cases, under-diagnosis and doctors not willing to report occupational cases due to legal influences, e.g. workers' compensation system.[60]

The Swedish scheme is a system for registration of workers' own reports and claims about occupational asthma as well as other occupational diseases. All claims on occupational diseases are listed in the Swedish Register of Reported Occupational Diseases (SRROD). When claiming that they have an occupational disease, workers have to complete a form with information regarding diagnosis, causes, current workplace and some basic personal information. The claim form has to be countersigned by the employer. The validity of asthma diagnosis could not be ascertained so over-estimation of asthma could happen. High risk occupations, as in other countries, included bakers, chemical processors and plastic workers. High risks were also found in occupations with less well recognised risks of asthma, such as welders and foundry workers. This may reflect patterns of reporting but a real increased risk cannot be ruled out.[61]

Industries, occupations and agents reported to these schemes vary by country but there are agents common to all. Most common agents are isocyanates (mainly from spray painting), flour in bakery workers, latex in health care workers and wood in the manufacturing of wood products. On the other hand, countries with specific dominant industries will report specific agents associated with these industries. In Finland, the Finland Register of Occupational Diseases (FROD) report indicates that almost half of cases of occupational asthma arise in agriculture and manufacturing industries. The most common reported agents were animal epithelia, flours, grains and fodders.[62]

Despite likely under-reporting associated with voluntary reporting schemes, they have been useful in identifying types of exposures common in cases of occupational asthma and common industries where these cases arise. Consistency of common agents and industries across countries gives merit to the usefulness of the schemes and provides opportunity for different countries to learn from each other strategies of primary prevention in those industries identified.

C: Case series

Data on case series of occupational asthma are scarce. Although there have been surveillance studies of occupational respiratory diseases and occupational asthma, clinical case series of patients suffering from occupational asthma have largely been confined to groups of workers reacting to single specified agents.[63] A few case series in specific occupational medicine clinics have provided data on common industries, jobs and agents causing occupational asthma.

A recent study done in the New York State Occupational Health Clinics found that most patients with work-related asthma were employed in service and manufacturing industries. Commonest occupations were teachers, farm operators and construction workers; and the most common agents implicated in occupational asthma were dust, indoor air, mold and solvents.[64]

In Washington, a study by Wheeler et al, reported construction, shipbuilding, automotive repair, airplane manufacturing, paper and electronics manufacturing as the commonest industries that employed cases of occupational asthma. Common occupations included painters, plumbers, machine operators, construction labourers, cleaners, cooks, forestry workers, carpenters and ship fitters. Agents implicated were isocyanates, solvents, red cedar and other wood, corrosive agents, crabs, formaldehyde and welding fumes.[65]

Patterns of occupations, industries and causative agents differed by geographical location and type of industries common in that setting. There is however, more information for potential prevention of workplace exposures from identified industries.

1.2.1.2 South Africa

There have been no population studies in South Africa. A Surveillance of work-related and Occupational Respiratory Disease scheme (SORDSA) in South Africa has been a source of data for distribution and causes of work-related respiratory diseases until its demise in 2003. SORDSA was established in 1996. It was a national database with uneven reporting among provinces. Participating reporters were pulmonologists and occupational medicine practitioners. To increase information dissemination and overcome underreporting, occupational health nurses were added as reporters. This brought about questions as to the validity of diagnoses made by occupational health nurses. However, information on common agents and industries was still useful in describing the nature and extent of work-related respiratory diseases in

South Africa. In a report of the first two years[66] latex was the most frequently reported agent, followed by isocyanates and platinum salts.

Although there are few studies of occupational asthma in South Africa, a comprehensive but not exhaustive list of causative agents published by SORDSA, though slightly out of date, covers most common agents. A report covering the years 1997-1999 identified the most common asthma causing agents to be isocyanates, latex proteins, flour, grain and platinum salts.[67] The scheme had to be abandoned in 2002 due to lack of reporting. Other South African studies have reported occupational asthma in grain mill workers,[68-70] small bakeries in supermarkets,[71] health care workers exposed to latex [67, 72] and soybean workers.[73] Studies conducted in the seafood processing industry[74] identified allergens such as crab, prawn, shrimp, soya, *anisakis* and salmon in cases of occupational asthma. In poultry workers sensitization was confirmed to chicken feed, litter and faeces.[75] Spider mite allergy was responsible for work-related asthma symptoms in table grape farm workers; [76] and Locusta migratoria was found as a potent sensitizer in those exposed to migratory grasshopper.[77]

A high prevalence due to isocyanates was found in chemical processing plant[78] and in automotive spray painting.[79] In precious metal refineries, a 41% incidence of platinum salt sensitivity was reported in platinum refinery[80] (compared to 11% cumulative incidence in a vanadium plant), although the diagnostic criteria for occupational asthma relied on symptoms, a less strict measure.[81] A prevalence of between 3% and 7% was found in those exposed to wood dust (hardwood and softwood) in a furniture plant and sawmill plant respectively.[82]

Although studies employed different methodology and exposure assessment was crude, the data on causative agents are still valuable in terms of identifying industries for intervention.

1.2.2 Occupational asthma prognosis

As socioeconomic outcomes of occupational asthma have been discussed already, only health outcomes will be discussed here. The prognosis of occupational asthma depends largely on cessation of exposure to the offending agent, duration of exposure to sensitizers after symptom onset and severity of asthma at diagnosis.[20, 21, 28, 83]

Several studies that have shown that cessation of exposure led to better health outcomes have also highlighted workplace challenges in attaining exposure avoidance either by elimination of the exposure or by relocation of the affected worker. The reality is that in most instances,

diagnosis is delayed and workers start treatment late when the disease is so severe that complete recovery may not be attained. Once diagnosed, removal from exposure is beneficial in terms of symptoms and lung function improvement. However, it may not be practical to relocate workers in many workplaces and even if that could be arranged, there might be loss of income from position downgrade or from not being able to do overtime anymore. Fear of losing income may lead workers to opt to remain in exposed occupations particularly where compensation is inadequate to meet the financial loss. The focus should be on cessation or reduction of exposure and on early recognition of occupational asthma (early diagnosis) to start medical therapy as soon as possible; because outcome is better in workers who have shorter duration of symptoms before diagnosis.[84-87]

Reduction of exposure necessitates identification of exposure agents and specific industries in cases of occupational asthma, hence this study that aims to identify agents and industries implicated in cases of occupational asthma in cases referred to the NIOH Clinic.

1.3 Study aims and objectives

1.3.1 Aim

To describe cases of occupational asthma assessed at the Clinic from 1st January 1997 to 31st December 2007.

1.3.2 Objectives

1. To characterize occupational asthma cases assessed at NIOH Occupational Medicine Clinic from 1st January 1997 to 31st December 2007 in terms of:
    4. types of industries, occupations and agents
    5. duration of exposure prior to onset of occupational asthma
    6. time from onset of symptoms to diagnosis
    7. nature of exposure e.g. intermittent, daily, etc
2. To investigate factors influencing latency period in cases of sensitizer-induced asthma
3. To investigate factors influencing lag time to diagnosis in cases of sensitizer-induced asthma

CHAPTER TWO: MATERIALS AND METHODS

In this section, the study design and method of selection of participants are described. Detailed descriptions of case definitions with criteria for inclusion into the study and data management are outlined. The chapter ends with ethical issues related to the study.

2.1 STUDY DESIGN

This is a descriptive study of cases of occupational asthma assessed by Clinic doctors at the NIOH Occupational Medicine Clinic from 1997 to 2007.

2.2 STUDY POPULATION AND SAMPLING (APPENDIX A)

All possible cases of occupational asthma diagnosed from 1st January 1997 to 31st December 2007 by NIOH doctors were identified from the Clinic's database. The Clinic has an electronic database of cases assessed at the Clinic since 1991. Data captured in the database includes patient's demographic data, referrer's details, occupational history, medical history including medical investigations, final diagnosis and compensation submission information. The database enables one to trace a patient based on South African identity number or passport number for foreign nationals and name and surname. Cases were identified by searching the database for cases which had a preliminary diagnosis of occupational asthma for the years 1997 to 2007. Search terms included, asthma, occupational asthma, irritant-induced asthma, RADS, Reactive Airway Dysfunction Syndrome, Bronchitis, COPD, Chronic Obstructive Airway Diseases and Chronic Obstructive Pulmonary Diseases. The following additional information was extracted from the database: identification number, name, surname, clinic unique number, year of diagnosis and occupational diagnosis. A total of 730 records were identified. Of these, one hundred and fifty seven (157) cases were identified as possibly having occupational asthma. Because the database contains selected information only, medical records (files) of 157 identified cases were retrieved to get comprehensive exposure information. Seventeen (17) doubtful cases were presented at the NIOH Occupational Medicine clinical meeting for a consensus decision as to whether they qualified to be included in the study. The panel was made up of 3 occupational medicine practitioners with more than 5 years' experience in occupational medicine. For consistence, the same panel decided on all cases. The panel accepted a further two cases from the doubtful group. The final number of cases included in the database was 142. Appendix 1 shows the process of selection of these cases.

Exclusion criteria

Of the 157 cases, 15 were excluded because:

- The case had pre-existing asthma aggravated by workplace exposures, i.e. work-exacerbated asthma, or
- There was no objective evidence of asthma, or
- The case was not resolved because of loss to follow-up, or
- The exposure agent was not an established cause of occupational asthma, or
- The case was exposed to long term low-dose irritants, thus not fulfilling the inclusion criterion of a once-off high exposure to respiratory irritants.

Thus 142 cases were left for study. These were divided into sensitizer and irritant- induced cases as shown below.

Sensitizer- induced asthma

Of the total 142 confirmed cases of occupational asthma, 131 had a convincing diagnosis of sensitizer-induced asthma based on medical records showing:

- Objective evidence of asthma as defined by reversible airflow limitation or supported by a positive metacholine challenge test showing non-specific bronchial hyper responsiveness. In this Clinic, a rather specific approach of a post-bronchodilator change in FEV_1 of 15% (as opposed to 12% recommended by South African Thoracic Society) or more and 200ml was considered significant. The 15% criterion was used previously as a diagnostic criterion hence maintained its usage for consistency. A metacholine challenge test was considered positive when a fall of 20% in FEV1 was induced by a concentration of 8mg/ml or less
- Confirmed workplace exposure to an established cause as listed by Chan-Yeung et al. (2006).[33] Temporal association with work i.e. development of asthma after exposure to a particular agent encountered in the workplace and presence of symptoms related to exposure

Irritant-induced asthma

Eleven (11) cases were considered irritant induced asthma as they satisfied the following criteria according to the American College of Chest physicians' consensus statement.[28]

- Absence of pre-existing asthma symptomatology, or a history of asthma in remission and exclusion of conditions that can simulate asthma
- Acute onset of asthma following a single once-off very high exposure to workplace irritants
- Exposure is to an irritant vapor, gas, fumes, or smoke in very high concentrations
- The onset of asthma symptoms develops within minutes to hours and < 24 hours after exposure
- There is a positive metacholine challenge test finding or equivalent, which signifies hyperactive airways
- There may or may not be airflow obstruction confirmed with pulmonary function testing
- There is exclusion of another pulmonary disorder that explains the symptoms and findings

Occupations and industries were categorized according to a known standard classification lists.[88] Industry classification system used was a standard system from the Compensation Fund in Pretoria. The classification list uses a rating system dividing employers into 23 classes based on business operations.

2.3 DATA CAPTURE

A data capture sheet (Appendix B) was used to collect the following data: clinic number, age, sex, company name, industry type, occupation, exposure agents, intensity and frequency of exposure, specific diagnosis and smoking history.

Additional clinical data, although not specifically recorded on the data capture sheet, were available to confirm diagnosis. Such data included spirometry, metacholine challenge test, skin prick test, RAST tests, serial peak flow measurements where available, and any supporting data to confirm occupational asthma and exclude other conditions.

2.4 DATA PROCESSING METHODS AND DATA ANALYSIS

A database was created using Epi Info (version 3.2) statistical software package. The researcher captured the data from the data capture sheet. After double entry and verification in Epi Info, cleaned data were analysed to address the objectives of the study. All analyses were carried out in STATA software version 10. Results were presented using simple descriptive statistics. Continuous variables were summarized using means and standard deviations. Categorical variables were described using proportions (percentages) and results were displayed in tables and graphs. Age was categorised into groups and summarized as such.

To test for statistical difference of summary statistics, chi-square (X^2) was used. Mann-U-Whitney and Kruskal-Wallis tests were used for continuous variables which were not normally distributed.

Independent variables used were age, sex, smoking, frequency of exposure, exposure agents and industry groups. The outcome variables, latency period and time to diagnosis were continuous in time-to-event measured in months. They were described using summary statistics and Kaplan-Meier survival curves. To assess crude relationships between the independent variables and the study outcomes, bivariate analyses were done using the log-rank test as a test of equality to assess which of the categorical variables were significant. Kaplan-Meier curves of the outcomes were plotted by independent variables to graphically display the relationships.

Multivariate analysis: This was a secondary data analysis as such variables were limited to data available from the Clinic records. Variables were fitted into the model as they were thought to be potential predictors based on literature. Most of the variables were fitted to the model to obtain adjusted estimates and to identify important predictors. Occupations were excluded because they could not be grouped into meaningful categories due to the varied nature of the jobs.

Unadjusted estimates of these important variables are presented in Section 5 before the multivariate model. Two models were constructed for both outcomes. The final model, Cox regression, included most variables. No additional refinement of the model was carried, because the size of data was too small to obtain meaningful results.

All analyses were carried out at an alpha level of 0.05: p-values less than 0.05 were interpreted as statistically significant. Hazard ratios were reported along with their 95% confidence intervals.

2.5 ETHICS

Ethical approval was granted by the University of the Witwatersrand Human Research Ethics Committee (Medical). Ethics approval letter attached (Appendix 3). For confidentiality, codes known only to the project manager were used to conceal patient identity; no reference can be made to the file or patient. No names or any form of identification are revealed in results or any published materials. Recommendations will be to individual industries without mention of the name of the company but rather a group in which that industry is classified.

CHAPTER THREE: RESULTS

In this chapter, 142 cases of occupational asthma are described. Details of industries, jobs and agents implicated in occupational asthma are presented. The 131 cases of sensitizer- induced asthma are described separately from the eleven irritant -induced asthma cases. Survival and multivariate analysis were performed to test associations between latency period and each specific determinant. This has been repeated for time to diagnosis and its determinants. Finally, a model using Cox regression was run for both outcomes, namely latency period and time to diagnosis.

SECTION 1: DESCRIPTION OF ALL 142 OCCUPATIONAL ASTHMA CASES

Table 1.1 summarises the cases according to general characteristics including the type of asthma. In this case series, the majority (82%) of cases were males and just over 40% of cases were younger than 40 years with the youngest patient being 25 years old and the eldest 62 years old. Mean age of both males and females = 43 years. As expected, the majority of cases (92%) were sensitizer-induced asthma and most of them were exposed to low-molecular weight agents. A quarter of the cases were current smokers and they were all men.

Table 1.1 Sex, age, smoking status and type of occupational asthma of 142 cases diagnosed at NIOH Clinic from 1997 - 2007

Characteristic	Total N (%)	Sensitizer – induced asthma (n =131) n (%)
Sex		
Male	116 (81.7)	108 (82.4)
Female	26 (18.3)	23 (17.6)
Age		
21- 30	14 (9.9)	12 (9.2)
31- 40	46 (32.4)	41 (31.3)
41- 50	49 (34.5)	46 935.1)
51- 60	31(21.8)	30 (22.9)
60+	2 (1.4)	2 (1.5)
Smoking status*#		
Current smoker	36 (26.1)	35 (26.7)
Non-smoker	105 (73.9)	95 (73.3)
Type of asthma		
Sensitizer	131 (92.2)	
Irritant	11 (7.8)	
Total	**142 (100)**	**131 (100)**

** The non- smoker category includes ex-smokers and those who never smoked at all.*
 # Smoking history is missing for 2 cases.

Somewhat surprisingly, only 14 cases (9.9%) were 30 years or younger; and only 12 cases (9.2%) in the sensitizer-induced group.

The 142 occupational asthma cases are described below in terms of industry and job. As can be seen from Table 1.2, the top five industries, responsible for the majority of occupational asthma cases, were Engineering, Chemical, Food, Smelter and Foundry sectors.

Table 1.2 Occupational asthma cases by industry

Industry	N (%)
Engineering	34 (23.9)
Chemical	22 (15.5)
Food	18 (12.7)
Foundry	16 (11.3)
Smelter	16 (11.3)
Transport	8 (5.6)
Social services	6 (4.2)
Other manufacturers	6 (4.2)
Agriculture	4 (2.8)
Cleaning	4 (2.8)
Mining	4 (2.8)
Clay & ceramics	2 (1.4)
Construction	1 (0.7)
Power	1 (0.7)
Total	**142 (100)**

General workers, machine operators and spray painters were the most common job categories (Table 1.3). The General workers category consisted of unskilled workers which included labourers who worked in a variety of industries. The category of “other” comprised an aircraft trimmer, two nurses, a plant sampler and a hairdresser.

Table 1.3 Occupational asthma cases by type of job

Type of job	N (%)
General worker	23 (16.2)
Machine operator	21 (14.8)
Spray painter	19 (13.4)
Technical staff	13 (9.2)
Fitter	11 (7.7)
Welder	8 (5.6)
Clerical & sales	7 (4.9)
Bakery staff	6 (4.2)
Moulder	6 (4.2)
Other*	5 (3.5)
Grinder	4 (2.8)
Mixer	4 (2.8)
Building artisan	3 (2.1)
Core maker	3 (2.1)
Electrician	3 (2.1)
Forklift driver	3 (2.1)
Kiln operator	3 (2.1)
Total	**142 (100)**

*****_The category "Other" includes nurses (2), aircraft trimmer (1), plant sampler (1) and hairdresser (1)._

SECTION 2: SENSITIZER-INDUCED ASTHMA CASES

2.1 Industry, type of job and exposure agents for 131 cases of sensitizer-induced asthma

As shown above in Table 1.1, there were 11 cases of irritant- induced asthma. These will be described separately in Section 6 at the end of the Results section. The following data are for the 131 cases of sensitizer-induced occupational asthma.

Table 2.1 Distribution of 131 cases of sensitizer-induced asthma by industry and agents

Industry	Agents					Total
	Isocyanates	Welding	Vanadium	Wheat	Other	
Engineering	14	9	0	0	9	**32**
Chemical	4	1	0	0	14	**19**
Smelter	0	1	15	0	1	**17**
Food	0	0	0	9	7	**16**
Foundry	2	5	0	0	7	**14**
Transport	3	2	0	0	2	**7**
Other manufacturer	2	0	0	0	4	**6**
Social Services	1	0	0	0	4	**5**
Agriculture	0	0	0	0	4	**4**
Cleaning	0	0	0	0	4	**4**
Mining	0	0	2	0	2	**4**
Clay & Ceramics	0	0	0	0	1	**1**
Construction	1	0	0	0	0	**1**
Power	0	1	0	0	0	**1**
Total	**27**	**19**	**17**	**9**	**59**	**131**

According to Table 2.1, the top five industries generating cases were Engineering, Chemical, Smelter, Food and Foundry. The majority of cases of isocyanates sensitization came from the Engineering sector, followed by Chemical and Transport sectors.
Cases due to welding came mainly from Engineering and Foundry sectors. Fifteen vanadium sensitized cases originated from a vanadium smelter, accounting for the majority of vanadium cases in this series. As expected, wheat sensitization mainly occurred in the Food sector. The majority of cases in the Food industry came from small-scale bakeries, where they were exposed to baking ingredients.

Foundries are better known for silicosis so exposures implicated from foundries need special mention. They were chromium salts, formaldehyde, nickel sulphate, resins, isocyanates and welding fumes. Cases included in the Social Services category were from a City Council, Department of Health, hair salon, technikon and a coin security company.
The category of “Other” agents was big enough to warrant special mention. Table 2.2 below shows these agents by industry.

Table 2.2 "Other" agents shown in Table 2.1 by industry

	Agriculture	Chemical	Clay and ceramics	Cleaning	Engineering	Food	Foundry	Mining	Other manufacture	Smelter	Social services	Transport
Animal feed	1											
Artificial colourants						1						
Chicken litter	2											
Chromium salts		1			1		2					
Cleaning agents		1		3				2				
Cobalt					1							
Colophony		1										
Cooling oils					1							
Formaldehyde					1		1					
Grain dust	1											
Grass											1	
Latex											2	
Leather dust									1			
Methyl Ethyl Ketone*		1										1
Metal fumes		1										
Milk powder						1						
Nickel sulphate		1					1					
Oil mists					1							
Onion						1						
Paint vapour												1
Peanuts						1						
Persulphates											1	
Pthallic anhydride		2										
Platinum salts										1		
Polyethylene		1										
Polyvinylchloride		2										
Prepolymer		1										
Proteolytic enzymes		1										
Resins			1		3		3		1			
Rubber					1				1			
Solvents±		1		1		1						
Soybean						2						
Wood dust									1			
TOTAL	**4**	**14**	**1**	**4**	**9**	**7**	**7**	**2**	**4**	**1**	**4**	**2**

*****MEK = *Methyl Ethyl Ketone is not an accepted sensitizing agent. Refer to discussion for explanation.*

±Solvents are not established sensitizers but satisfied asthma diagnosis criteria. The two solvents were acetone, alkylphenoxy polyethoxyethanol and the third one was referred to only as a solvent.

Table 2.3 Type of job for 131 sensitizer-induced asthma cases

Type of job	n (%)
General worker	19 (14.5)
Machine operator	19 (14.5)
Spray painter	19 (14.5)
Fitter	11 (8.4)
Technical staff	11 (8.4)
Welder	8 (6.1)
Bakery staff	6 (4.6)
Clerical & Sales	6 (4.6)
Moulder	6 (4.6)
Other*	5 (3.8)
Mixer	4 (3.0)
Building artisan	3 (2.3)
Core makers	3 (2.3)
Forklift driver	3 (2.3)
Grinder	3 (2.3)
Kiln operator	3 (2.3)
Electrician	2 (1.5)
Total	**131 (100)**

**The job "Other" includes nurses (2), aircraft trimmer (1), plant sampler (1) and hairdresser (1).*

Not surprisingly, spray painters were among the commonest categories in this group, and coupled with general workers, machine operators, fitters and technical staff, accounted for the majority of cases of occupational asthma. The majority of the spray painters (12 of 19) originated from the Engineering sector.

Agents causing occupational asthma are generally classified into high molecular weight (HMW) and low molecular weight (LMW). In this series, the commonest exposure agents were from the low molecular weight category, making up 80.1% of cases. The top three agents were isocyanates, welding fumes and vanadium (Table 2.4).

Table 2.4 Exposure agents for 131 cases of sensitizer-induced asthma

Exposure Agents	n (%)
Low molecular weight agents	
Isocyanates	27 (20.6)
Welding fumes	19 (14.5)
Vanadium	17 (12.9)
Resins	8 (6.1)
Cleaning agents	6 (4.5)
Chromium salts	4 (3.1)
Solvents	3 (2.2)
Formaldehyde	2 (1.5)
MEK	2 (1.5)
Nickel sulphate	2 (1.5)
Phthallic anhydride	2 (1.5)
Polyvinylchloride	2 (1.5)
Artificial colourants	1 (0.8)
Cobalt	1 (0.8)
Colophony	1 (0.8)
Cooling oils	1 (0.8)
Metal fumes	1 (0.8)
Oil mists	1 (0.8)
Paint vapour	1 (0.8)
Persulphates	1 (0.8)
Platinum salts	1 (0.8)
Polyethylene	1 (0.8)
Prepolymer	1 (0.8)
High molecular weight agents	
Wheat	9 (6.8)
Chicken litter	2 (1.5)
Latex	2 (1.5)
Rubber	2 (1.5)
Soybean	2 (1.5)
Animal feed	1 (0.8)
Grain dust	1 (0.8)
Grass	1 (0.8)
Leather dust	1 (0.8)
Milk powder	1 (0.8)
Onion	1 (0.8)
Peanuts	1 (0.8)
Proteolytic enzymes	1 (0.8)
Wood #	1 (0.8)
Total	**131(100)**

#Wood classified as HMW, although some woods induce asthma by LMW compounds (e.g. plicatic acid in red cedar wood).

Within high molecular weight agents, plants accounted for the majority (77%) of exposures (Fig. 2.1). Examples here include wheat, grass, rubber and wood. Animal products like chicken litter, milk powder, and others were found in 19% of cases whilst proteolytic enzymes were seen in 4% of cases.

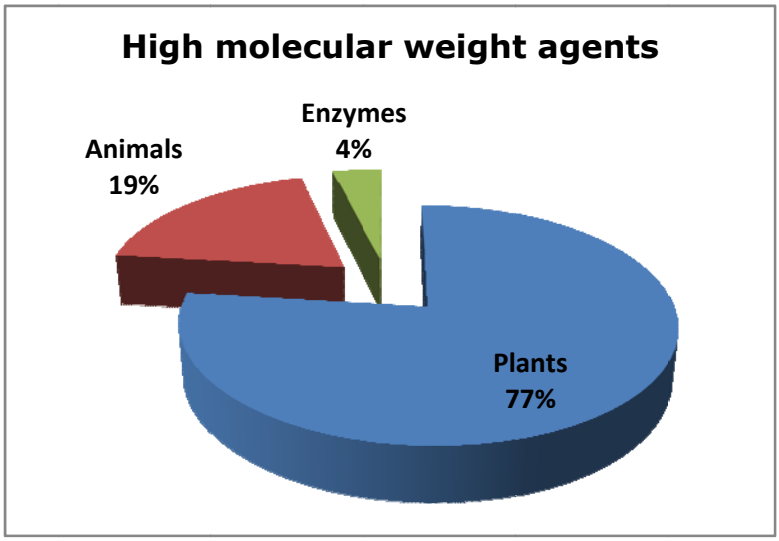


Figure 2.1 High molecular weight agents by origin

Figure 2.2 below shows frequency of exposure which was categorized into daily and less than daily, or less frequently. The majority (78%) of people were exposed daily to the offending agent.

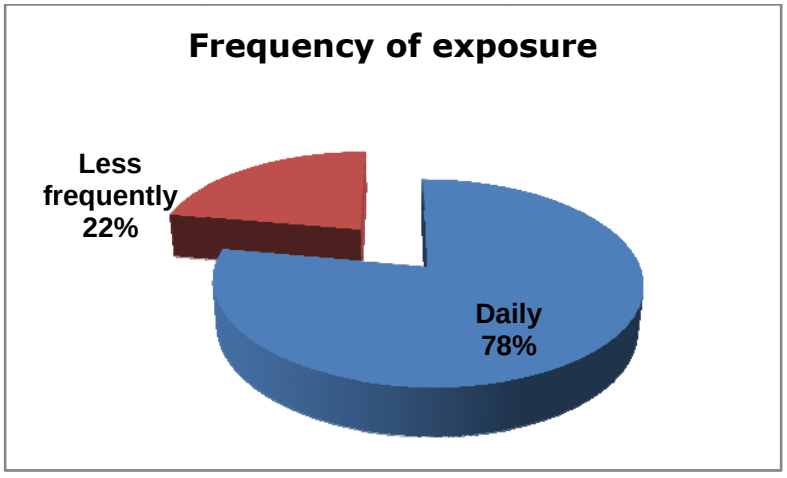
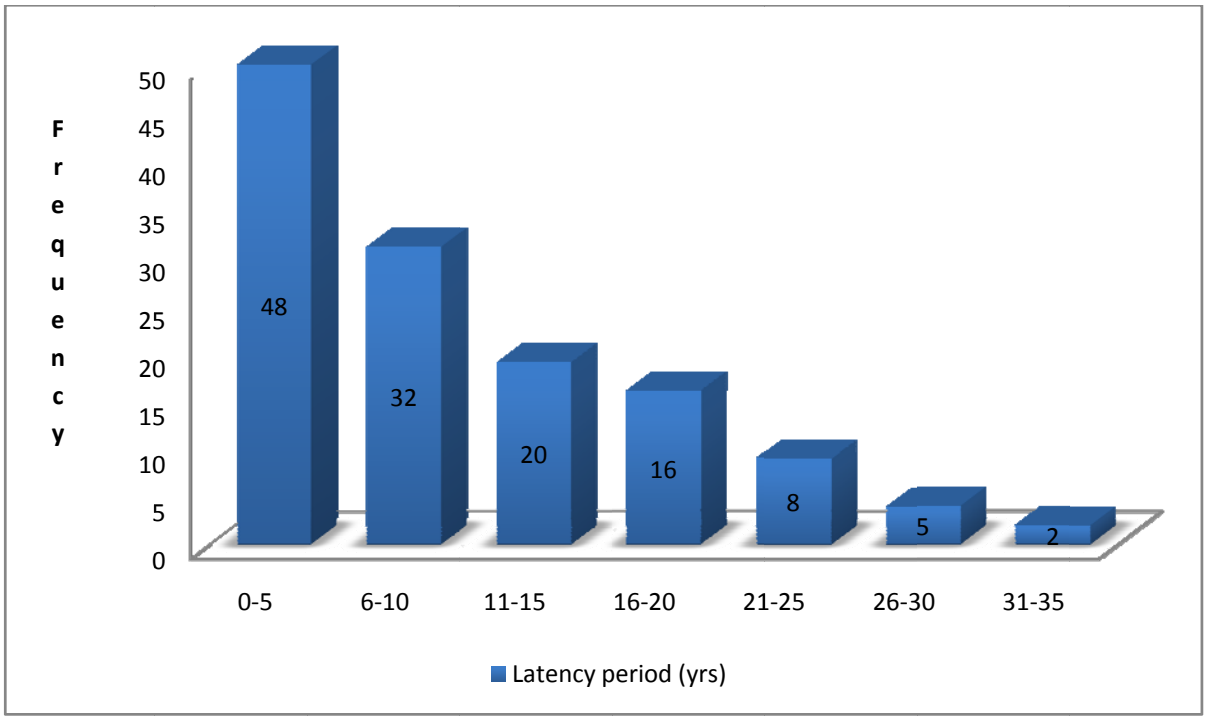


Figure 2.2 Distribution of frequency of exposure

SECTION 3: LATENCY PERIOD

Latency period in this context is the time from first exposure to the offending agent, to the development of symptoms. First, simple data on latency period are presented followed by associations of latency with specific determinants that might have an effect on latency.



Mean	Std Dev	Min	Max	Median	25%ile	75%ile
9.84	7.98	0.1	32.0	7.0	4.0	15.0

Figure 3.1 Distribution of latency period in years

Tables 3.1 to 3.6 show latency period, categorized into 12 months or less and more than 12 months. Tables 3.1, 3.3, and 3.5 shows latency by smoking, molecular weight of agent (LMW and HMW) and major industry respectively. The cut-point of 12 months was selected as annual periodic examinations are commonly recommended for surveillance of workers exposed to asthma-causing agents.

Tables 3.1 and 3.2 below describe the association between smoking and latency period.

Table 3.1 Latency period by smoking status

Smoking status	Latency period		Total	Chi-square
	</= 12 months	> 12 months		
Current smokers	4 (11.4%)	31 (88.6%)	**35**	**χ^2 =0.02**
Non-smokers	10 (10.5%)	85 (89.5%)	**95**	**p-value = 0.55**
Total	**14**	**116**	**130***	

**1 smoking history missing.*

The majority of cases were non- smokers. There were no women current smokers.

Table 3.2 Latency period in years by smoking status

	N	Mean (SD)	Median	Min - Max	Test
Current Smokers	35	8.46 (7.54)	6.0	0.1 - 28	**Mann-U- Whitney**
Non-smokers	95	10.37 (8.16)	8.0	0.1 - 32	**p = 0.202**
					Z = 1.276

Mann Whitney test was used because data is not normally distributed.

Latency period for current smokers was two years shorter than non-smokers.

Table 3.3 Latency period by high or low molecular weight agent

Type of Agent	Latency period		Total	Chi-square
	</=12 months	>12 months		
LMW	12 (11.4%)	93 (88.6%)	**105**	**X^2 = 0.20**
HMW	2 (7.7%)	24 (92.3%)	**26**	**p-value = 0.582**
Total	**14**	**117**	**131**	

The majority of cases in both categories (HMW and LMW) reported symptoms after the first year of exposure.

Table 3.4 Latency period in years by type of agent (high versus low molecular weight)

	N	Mean (SD)	Median	Min - Max	Test
LMW	105	9.94 (8.12)	8.0	0.1 – 32	**Mann-U-Whitney**
HMW	26	9.42 (7.52)	7.0	0.1 - 27	**p =0.869**
					Z =0.165

Data not normally distributed so Mann Whitney test used.

The type of exposure agent has been reported as a factor in determining time to symptom development. Although not statistically significant, the latency period, that is, time from first exposure to development of symptoms, people exposed to HMW agents reported symptoms 1 year earlier than those who were exposed to LMW agents.

Table 3.5 Latency period by four most common agents

Agent	Latency period		Total	Chi-square
	</=12 months	**>12 months**		
Isocyanates	6 (22.2%)*	21 (77.8%)	**27**	**χ^2 =6.47**
Welding	0 (0.0%)	19 (100%)	**19**	**p-value =0.166**
Vanadium	1 (5.9%)	16 (94.1%)	**17**	**DF = 4**
Wheat	1 (11.1%)	8 (88.9%)	**9**	
Other	6 (10.2%)	53 (89.8%)	**59**	
Total	**14**	**117**	**131**	

**Row percent*

There were no significant differences observed in latency period among various types of exposure agents as shown in Table 3.5. However, it is noted that of those exposed to welding fumes, none reported symptoms within the first year of exposure.

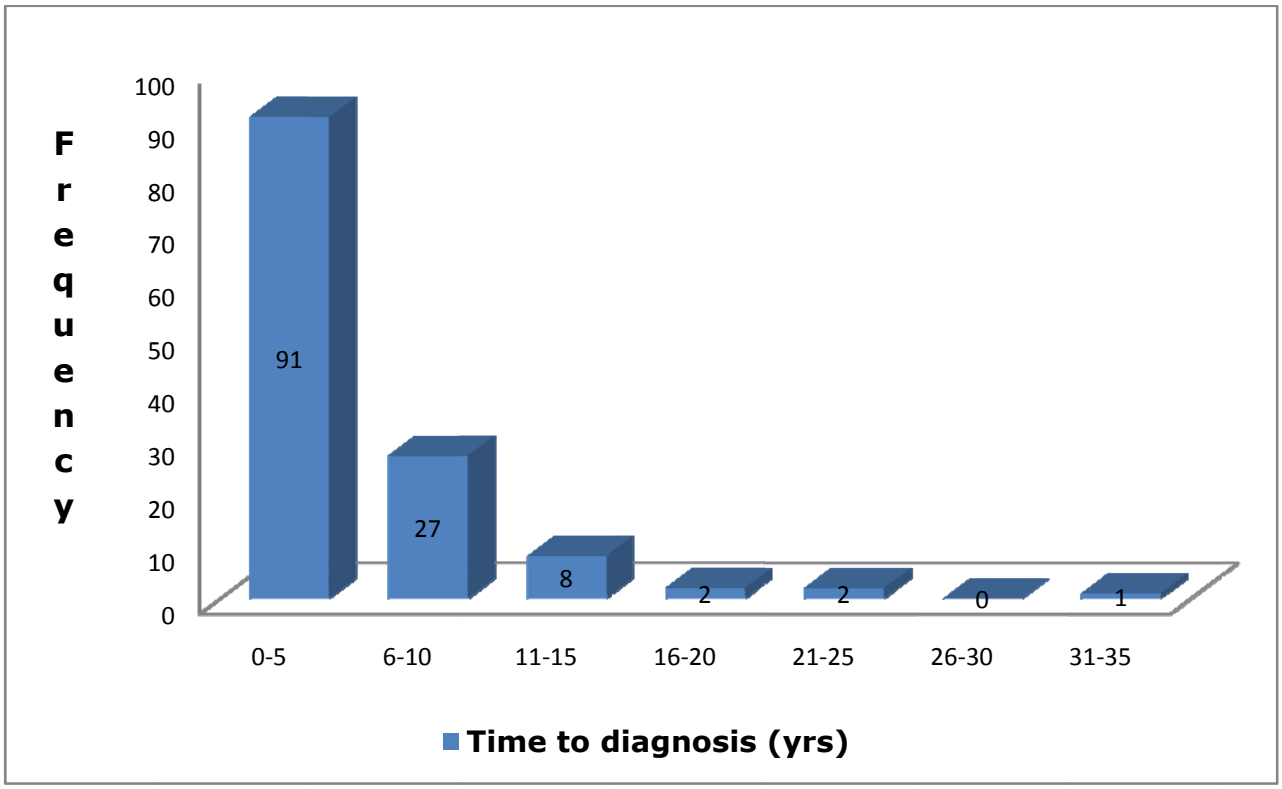
Table 3.6 Latency period in years by four most common agents

Agent	N	Mean (SD)	Median	Min - Max	Kruskal-Wallis
Isocyanates	27	8.60 (8.15)	7.0	0.1 - 29	
Welding	19	12.26 (9.10)	9.0	3 - 32	**Critical value = 3.009**
Vanadium	17	9.59 (7.90)	8.0	0.1 – 30	**p-value = 0.556**
Wheat	9	11.33 (8.51)	10.0	1 - 27	
Other	59	9.47 (7.55)	7.0	0.1 - 32	

Although there was no statistically significant difference in latency period, isocyanates seemed to induce symptoms earlier than the other three most common agents.

SECTION 4: TIME TO DIAGNOSIS

The time from development of symptoms to diagnosis is described here simply as time to diagnosis. As for latency period, time to diagnosis was also catergorised into 12 months or less and more than 12 months. First, simple data for time to diagnosis are presented followed by associations with possible determinants. The following tables present data on smoking, type of sensitizing agent and the four most common agents.



Mean	Std Dev	Min	Max	Median	25%ile	75%ile
4.85	5.3	0.1	32.0	3.0	1.0	6.0

Figure 4.1 Distribution of time to diagnosis in years

About 50% of cases were diagnosed within 3 years of having reported symptoms. However, it is notable that it took over 10 years for 13 cases to be diagnosed.

Table 4.1 Time to diagnosis by smoking status

Smoking status	Time to diagnosis		Total	Chi-square
	</= 12 months	**> 12 months**		
Current smokers	5 (14.3%)	30 (85.7%)	**35**	**χ^2 = 2.07**
Non-smokers	25 (26.3%)	70 (73.7%)	**95**	**p-value = 0.15**
Total	**30**	**100**	**130***	

**1 smoking history is missing.*

A larger, but non-significant, proportion of smokers were diagnosed after having symptoms for longer than 12 months (85.7% versus 73.7% in non-smokers).

Table 4.2 Time to diagnosis in years by smoking

	N	Mean (SD)	Median	Min - Max	Test
Current Smokers	35	5.46 (4.16)	4.0	1 - 15	**Mann –U- Whitney**
Non-smokers	95	5.03 (5.77)	3.0	0.1 - 32	**p = 0.151**
					Z = 1.436

Table 4.3 Time to diagnosis by high or low molecular weight agent

Type of Agent	Time to diagnosis		Total	Chi-square
	</=12	**> 12 months**		**χ^2 =0.25**
LMW	25 (23.8%)	80 (76.2%)	**105**	**p-value = 0.620**
HMW	5 (19.2%)	21 (84.0%)	**26**	
Total	**30**	**101**	**131**	

Only about 20% of cases in each category were diagnosed within one year of developing symptoms.

Table 4.4 Time to diagnosis in years by type of agent (HMW versus LMW)

	N	Mean (SD)	Median	Min - Max	Test
LMW	105	5.46 (5.58)	4.0	0.1 – 32	**Mann-U-Whitney**
HMW	26	3.74 (4.14)	2.0	0.1 - 18	**P = 0.141**
					Z = 1.471

On average it took about 5.4 years to get diagnosed for cases exposed to LMW in comparison to 3.7 years for HMW. This difference is not statistically significant.

Table 4.5 Time to diagnosis by four most common agents

Agent	Time to diagnosis		Total	Chi-square
	</=12 months	**>12 months**		
Isocyanates	7 (25.9%)	20 (74.1%)	27	**χ^2 =4.84**
Welding	4 (21.0%)	15 (79.0)	19	**Df = 4**
Vanadium	1 (5.9%)	16 (94.1%)	17	**p-value = 0.304**
Wheat	1 (11.1%)	8 (88.9%)	9	
Other	17 (28.8%)	42 (71.2%)	59	
Total	**30**	**101**	**131**	

Table 4.6 Time to diagnosis in years by four most common agents

	N	Mean (SD)	Median	Min - Max	Kruskal-Wallis
Isocyanates	27	5.66 (5.24)	5.0	0.5 – 23	
Welding	19	4.32 (3.89)	3.0	0.1 - 15	**Critical value =4.13**
Vanadium	17	5.53 (2.83)	5.0	1.0 – 10	
Wheat	9	3.60 (2.40)	4.0	0.2 - 7	**p-value = 0.388**
Other	59	5.24 (6.53)	2.0	0.1 - 32	

In the table above, the category “other agents” had the shortest time to diagnosis, 2 years, and welding fumes followed at 3 years in comparison to the other three most common agents.

SECTION 5: SURVIVAL AND MULTIVARIATE ANALYSIS

In this section, two multivariate analyses are presented for sensitizer-induced asthma cases. Independent variables used were age, sex, smoking, frequency of exposure, exposure agents and industry groups. The outcome variable, latency period was continuous in months. The same method was employed for time to diagnosis.

First, latency period analysis is presented followed by time to diagnosis analysis. The individual independent variables that were included in the models were age at exposure, sex and smoking; and occupational determinants were frequency of exposure, exposure agents and industry category. Crude bivariate analyses were done for each categorical determinant. Then the log-rank test was used as a test of equality to see which of the categorical variables were significant. Kaplan-Meier curves were plotted by independent variables. The final model, Cox regression included most variables listed above.

Below, all variables, including those that did not show significant associations, are described by graph and table. These determinants are age, sex, smoking, frequency of exposure, exposure agent and industry. And the final model is presented showing all variables, hazard ratios and confidence intervals.

5.1 Latency period

Note: only 129 cases are included in the analysis because of missing information for two records without date on when symptoms started.

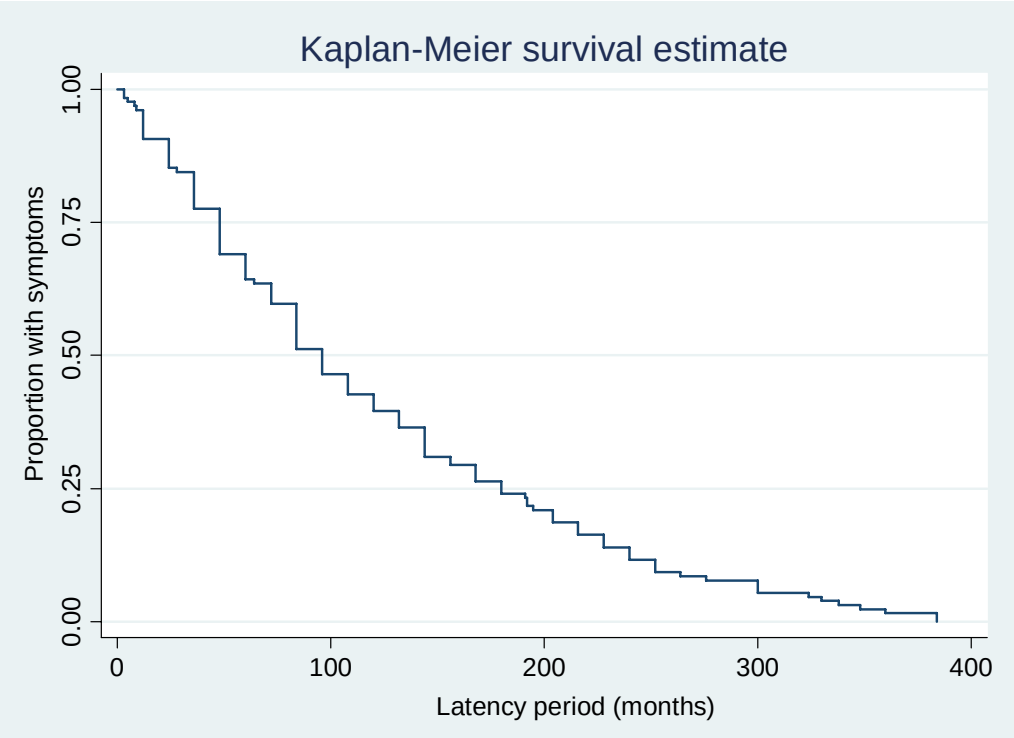


Figure 5.1.1 Latency period failure estimate for all 129 subjects with sensitizer induced asthma

Age at exposure

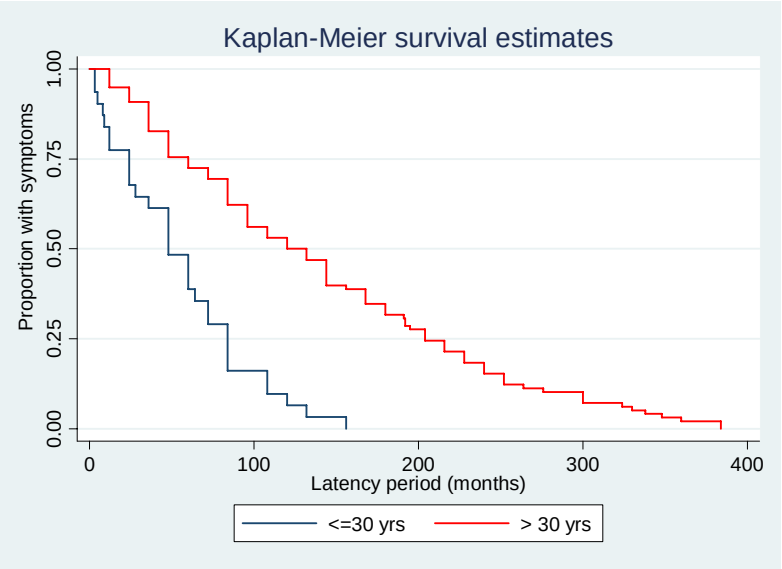


Figure 5.1.2 Latency period by age at exposure categorized into 1 </= 30 years and 2 is older than 30 years

Table 5.1.1 Log-rank test for equality of survivor functions for latency period by age at exposure

Age at exposure (yrs)	***Events***	
	Observed	Expected
</= 30	31	12.54
> 30	98	116.46
Total	**129**	**129**

chi2 (1) = 35.13

Pr>chi2 = 0.0000

Younger people had a significantly shorter latency period, suggesting that they reported developing symptoms sooner after exposure than older people.

Sex

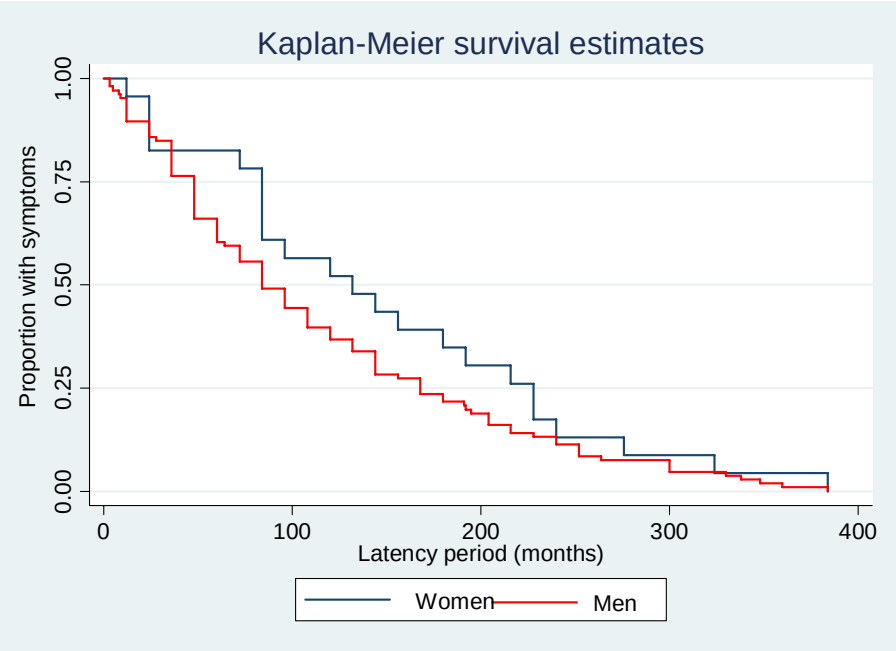


Figure 5.1.3 Latency period by sex

Table 5.1.2 Log-rank test for equality of survivor functions for latency period by sex

Sex	***Events***	
	Observed	Expected
Females	23	28.78
Males	106	100.11
Total	**129**	**129.00**

chi2 (1) = 1.73

Pr>chi2 = 0.1879

Although not statistically significant, our data shows that men reported developing symptoms earlier than women.

Smoking

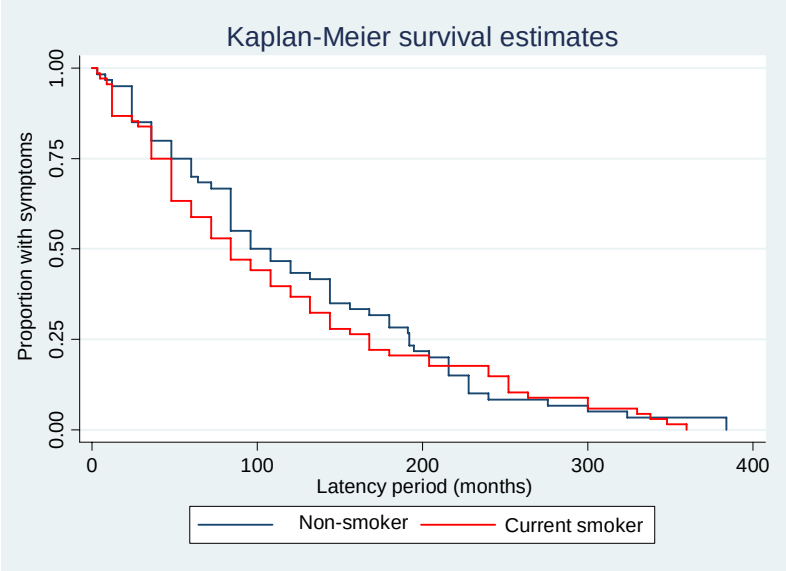


Figure 5.1.4 Latency period by smoking

Table 5.1.3 Log -rank test for equality of survivor functions for latency period by smoking

Smoking	***Events***	
	Observed	Expected
Non-smokers	60	63.45
Current smokers	68	64.55
Total	**128***	**128.00**

**1 smoking history missing.*

chi2 (1) = 0.41

Pr>chi2 = 0.5202

According to figure 5.1.4, current smokers seem to have a shorter latency than non-smokers, although this is not significant.

Frequency of exposure

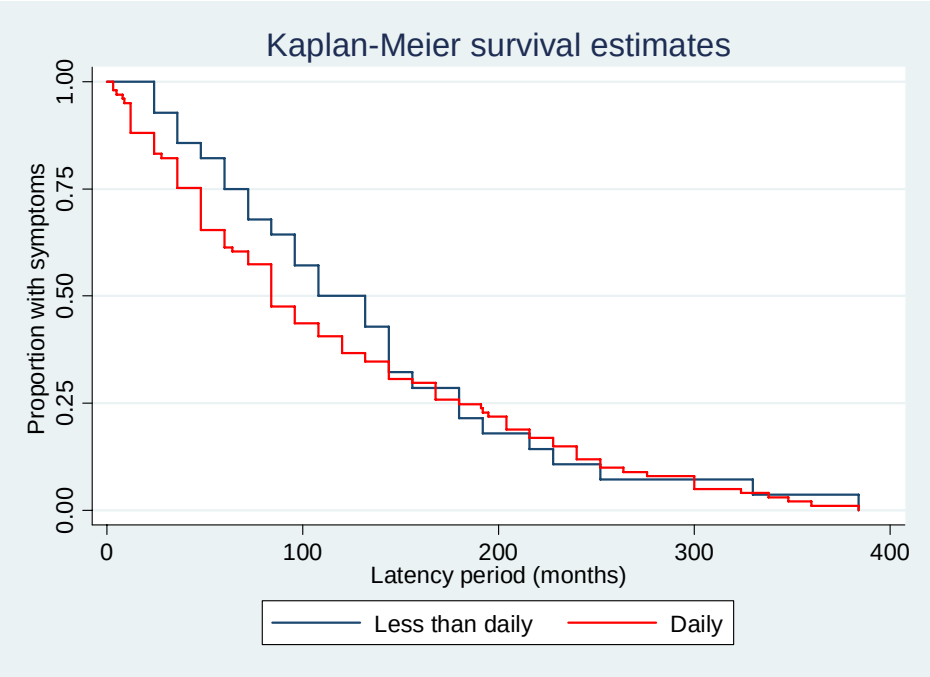


Figure 5.1.5 Latency period by frequency of exposure

Table 5.1.4 Log-rank test for equality of survivor functions for latency period by frequency of exposure

Frequency of exposure	***Events***	
	Observed	Expected
Less frequently	28	31.09
Daily	101	97.98
Total	**129**	**129.00**

chi2 (1) = 0.43

Pr>chi2 = 0.5103

There was no difference between frequency of exposure (those with daily and less than daily) and latency period.

Exposure agents

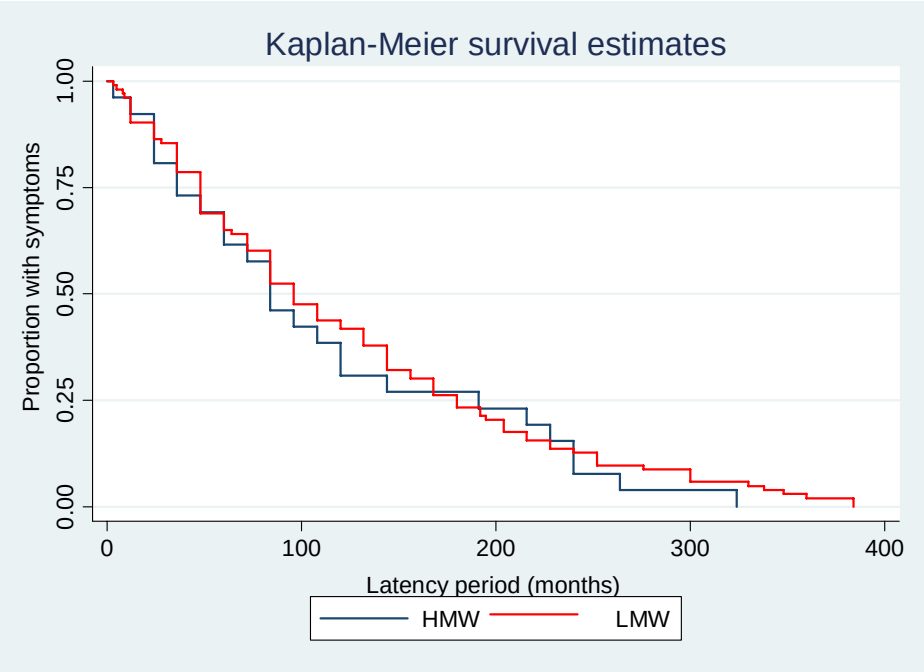


Figure 5.1.6 Latency period by type of exposure agent

Table 5.1.5 Log-rank test for equality of survivor functions for latency period by type of exposure agent

Exposure agents	***Events***	
	Observed	Expected
Low molecular weight	103	105.62
High molecular weight	26	23.38
Total	**129**	**129.00**

chi2 (1) = 0.39

Pr>chi2 = 0.5304

There was no statistical difference in the time taken to report symptoms from the time of first exposure to either high or low molecular weight agents.

Industry

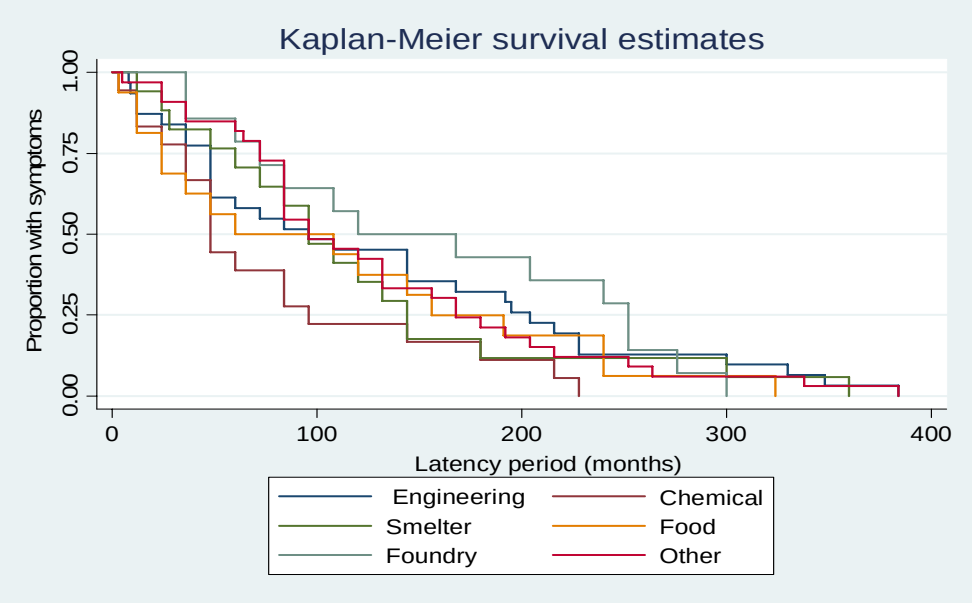


Figure 5.1.7 Latency period by type of industry

Table 5.1.6 Log-rank test for equality of survivor functions for latency period by industry type

Industry	*Events*	
	Observed	Expected
Engineering	31	34.46
Chemical	18	10.80
Smelter	17	16.33
Food	16	13.85
Foundry	14	18.28
Other	33	35.04
Total	**129**	**129.00**

chi2 (4) = 7.32

Pr>chi2 = 0.1982

The graph is difficult to interpret visually but clearly people from chemical industry seem to report symptoms earlier than those in other industries although this is not statistically significant.

Multivariate analysis: Cox regression model for latency period

The variables fitted into this model were decided upon apriori as they were thought to be potential predictors based on literature review irrespective of their statistical significance. The industry category was further grouped into five most common industry and others. The reference industry was the other group. Age at reporting of symptoms was categorised into 30years and younger or older than 30 years.

All variables were put in the model at the same time without prior adjustment for individual variables in other models.

Table 5.1.7 Multivariate analysis: Cox regression model for latency period by chosen variables

Variable	Hazard ratio	p-value	95% conf. interval
Sex	1.529	0.143	(0.87; 2.70)
Agents	1.153	0.680	(0.59; 2.28)
Smoking	0.960	0.856	(0.62; 1.48)
Engineering	0.988	0.967	(0.57; 1.71)
Chemical	2.032	0.029	(1.08; 3.84)
Smelter	1.062	0.850	(0.57; 1.99)
Food	1.093	0.819	(0.51; 2.35)
Foundry	0.788	0.478	(0.48; 1.66)
Age at symptoms	4.803	0.000	(2.47; 9.32)
Frequency of exposure	1.406	0.146	(0.89; 2.23)

Number of subjects = 128, LR chi2 (10) = 27.26, Log likelihood = -488.26249, Prob > chi2 = 0.0024.

In this model, age at start of symptoms and chemical industry group contributed significantly to the model. Cases older than 30 years of age were 4.8 times more likely to report symptoms later than younger ones. Cases from the chemical industry group were two times more likely to report symptoms earlier in comparison to other industry groups.

5.2 Time to diagnosis for selected events

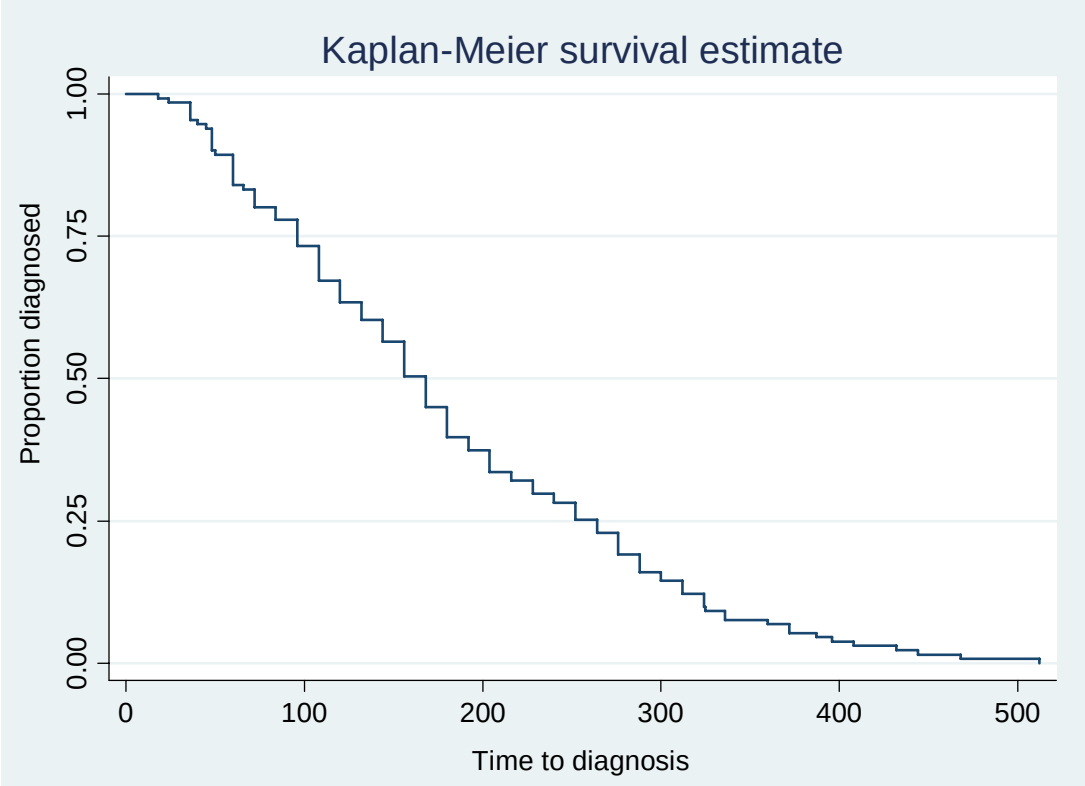


Figure 5.2.1 Time to diagnosis failure estimate for all 128 subjects with sensitizer induced asthma

Age at diagnosis

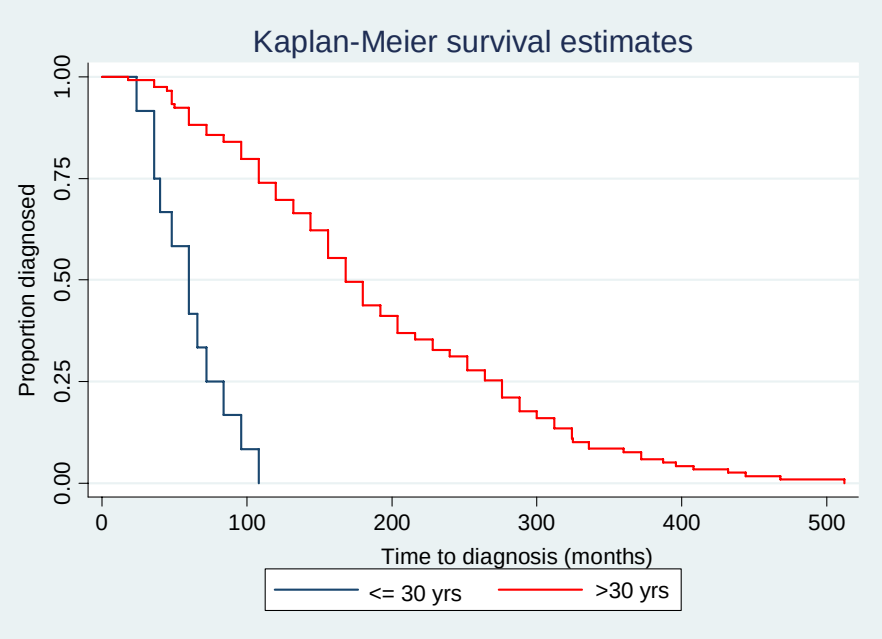


Figure 5.2.2 Time to diagnosis by age

Table 5.2.1 Log-rank test for equality of survivor functions for time to diagnosis by age at diagnosis

Age at diagnosis (yrs)	***Events***	
	Observed	Expected
<= 30	12	1.94
>30	119	129.1
Total	**131**	**131**

chi2 (1) = 57.11

Pr>chi2 = 0.0000

The graph above shows that 100% of young cases were diagnosed within ten years of having reported symptoms. This was statistically significant as shown by the p-value less than 0.05

Sex

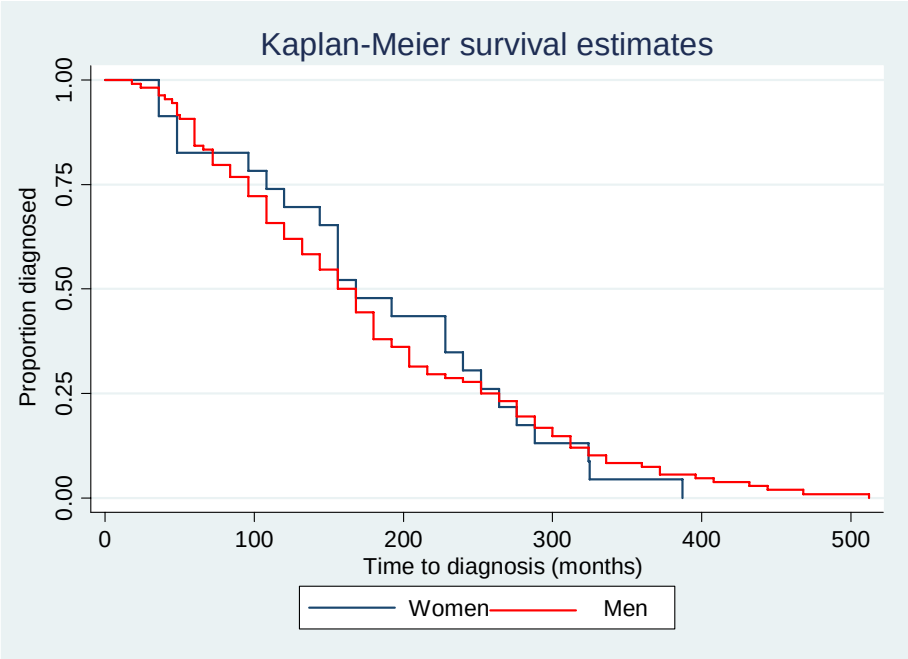


Figure 5.2.3 Time to diagnosis by sex

Table 5.2.2 Log-rank test for equality of survivor functions for time to diagnosis by sex

Sex	***Events***	
	Observed	Expected
Females	23	22.65
Males	108	108.35
Total	**131**	**131**

chi2 (1) = 0.01

Pr>chi2 = 0.9331

Although we saw sex differences with regards to latency period, this is not demonstrated for time to diagnosis.

Smoking

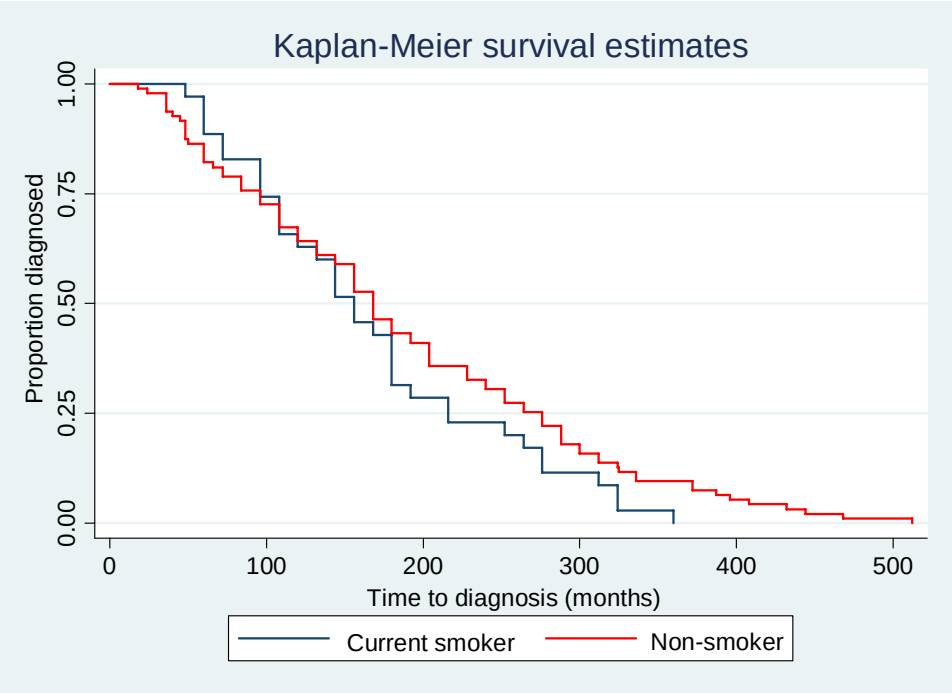


Figure 5.2.4 Time to diagnosis by smoking

Table 5.2.3 Log-rank test for equality of survivor functions for time to diagnosis by smoking

Smoking	***Events***	
	Observed	Expected
Current smokers	35	29.18
Non-smokers	95	100.82
Total	**130***	**130.0**

**1 smoking history missing.*

chi2 (1) = 1.65

Pr>chi2 = 0.1986

It looks like it took current smokers slightly less time to be diagnosed as compared to non-smokers but this is not statistically significant.

Frequency of exposure

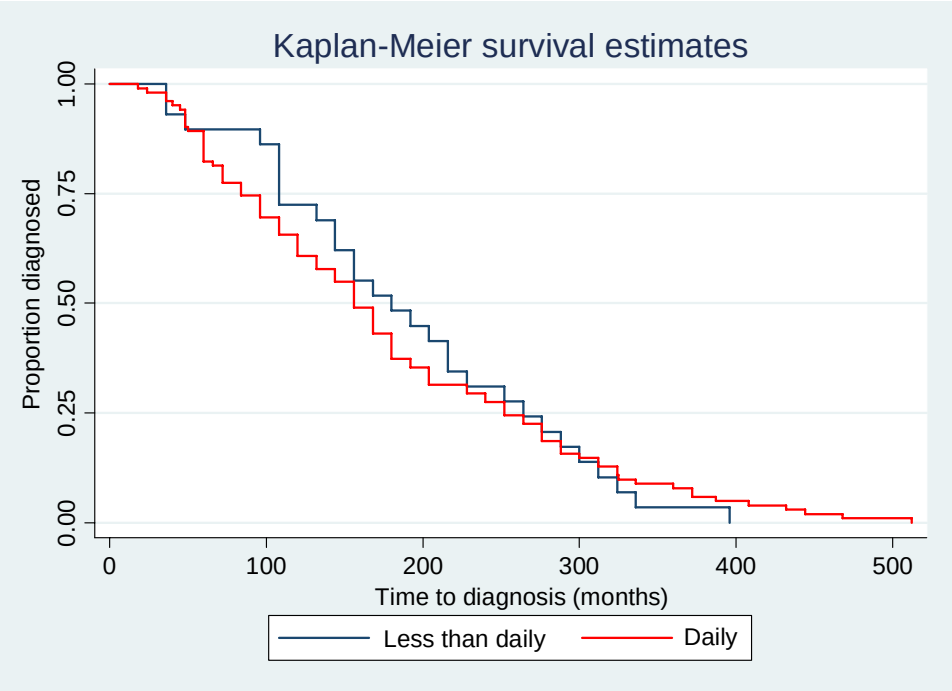


Figure 5.2.5 Time to diagnosis by frequency of exposure

Table 5.2.4 Log-rank test for equality of survivor functions for time to diagnosis by frequency of exposure

Frequency of exposure	***Events***	
	Observed	Expected
Less than daily	29	29.56
Daily	102	101.44
Total	**131**	**131**

chi2 (1) = 0.02

Pr>chi2 = 0.9025

There is no difference in time to diagnosis between those exposed daily and less frequently.

Exposure agents

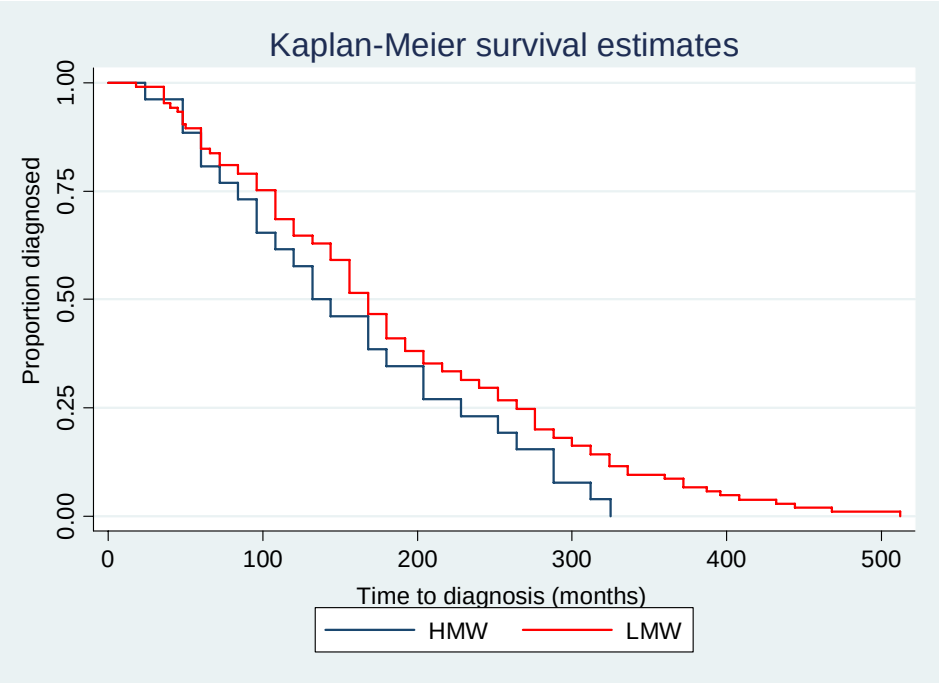


Figure 5.2.6 Time to diagnosis by type of agent

Table 5.2.5 Log-rank test for equality of survivor functions for time to diagnosis by type of exposure agents

Exposure agents	***Events***	
	Observed	Expected
Low molecular weight	105	110.81
High molecular weight	26	20.19
Total	131	131.00

chi2 (1) = 2.17

Pr>chi2 = 0.1412

Cases exposed to high molecular weight agents were diagnosed somewhat earlier than those exposed to low molecular weight agents**.**

Industry

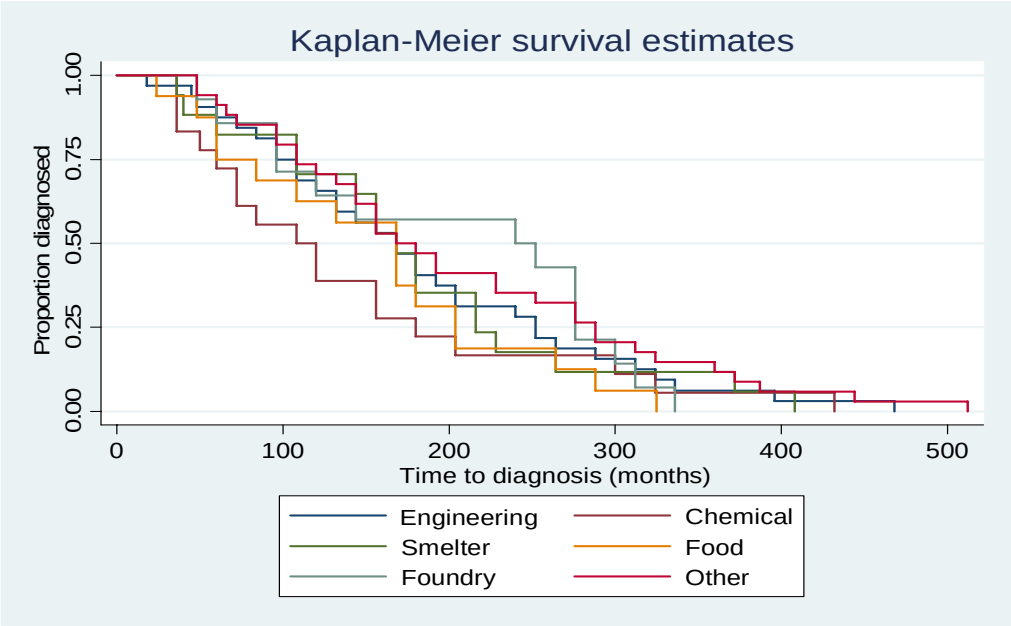


Figure 5.2.7 Time to diagnosis by type of industry

Table 5.2.6 Log-rank test for equality of survivor functions for time to diagnosis by industry type

Industry	***Events***	
	Observed	Expected
Engineering	32	32.24
Chemical	18	13.17
Smelter	17	16.26
Food	16	12.30
Foundry	14	15.43
Other	34	41.59
Total	**131**	**131.00**

chi2 (5) = 4.84

Pr>chi2 = 0.4351

Although it is difficult to interpret the above graph due to 6 industrial groups, cases from the chemical industrial group were diagnosed earlier than the other groups.

Multivariate analysis: Cox regression model for time to diagnosis

Multivariate model: The variables fitted into this model were decided upon apriori as they were thought to be potential predictors based on literature review irrespective of their statistical significance. The industry category was further grouped into five most common industry and others. The reference industry was the other group. Age at reporting of symptoms was categorised into 30years and younger or older than 30 years.

All variables were put in the model at the same time without prior adjustment for individual variables in other models.

Table 5.2.7 Multivariate analysis: Cox regression model for time to diagnosis by chosen variables

Variable	Hazard ratio	p-value	95% conf. interval
Sex	0.818	0.441	(0.49; 1.36)
Agents	1.631	0.170	(0.81; 3.28)
Smoking	0.853	0.474	(0.55; 1.32)
Engineering	1.625	0.072	(0.96; 2.75)
Chemical	2.124	0.020	(1.13; 4.00)
Smelter	1.506	0.200	(0.81; 2.82)
Food	1.277	0.546	(0.58; 2.82)
Foundry	1.348	0.380	(0.69; 2.62)
Age at symptoms	0.095	0.000	(0.05; 0.20)
Frequency of exposure	1.142	0.557	(0.73; 1.78)

Number of subjects = 130, LR chi2 (10) = 38.42, Log likelihood = -491.01462, Prob > chi2= 0.0000.

In the model, important predictors of early diagnosis were age and chemical industry. People younger than 30years of age and those employed in chemical industry were diagnosed earlier.

SECTION 6: IRRITANT- INDUCED ASTHMA CASES

Eleven cases satisfied the criteria for irritant – induced asthma as stipulated by Chan- Yeung et al.[31] Table 6.1 summarises some of the features of these cases. All cases had no previous history of asthma and experienced symptoms within 24 hours of exposure to a high concentration of the agent. For those cases that were on treatment and lung function tests were within normal limits, the diagnosis was supported by the presence of nonspecific bronchial hyper responsiveness. The majority of cases were non-smokers except for 2 current smokers and one ex-smoker. A more detailed description of the cases follows.

Table 6.1 Characteristics of irritant-induced asthma cases: sex, age, smoking history, type of exposure agent and occupation

Case	Sex	Age	Smoking status	Type of job	Agent
1	Female	37	Non smoker	Packer	Cleaning agents
2	Female	34	Non smoker	Off setter	Methane
3	Male	29	Non smoker	Technician	Hydrofluoric acid
4	Male	34	Smoker	Electrician	Paint vapours
5	Male	45	Non smoker	Cleaner	Turpentine
6	Male	41	Ex smoker	Brazing	Acetylene gas
7	Male	39	Non smoker	Technical officer	Irritant gas
8	Male	38	Smoker	Security officer	PVC fumes
9	Female	30	Missing	Secretary	Diazinon
10	Male	42	Non smoker	Packer	Phosphoric acid
11	Male	56	Non smoker	Machine operator	Cyanuric chloride

Case 1 involved a one-time high exposure to an unknown irritant cleaning chemical with a strong vinegar smell that was used in an adjacent department. Throat and chest symptoms were experienced on the same day and were severe enough to warrant a week's admission to hospital. Diagnosis was made several months later because of internal company disputes as to the nature of exposure. The case was accepted under COID Act as irritant-induced asthma.

Case 2 also had typical chest symptoms within the same day of exposure to methane and other gases due to an electrical fault. She was rushed to hospital after collapsing and not being able to breathe. Since then, chest tightness and cough persisted and were aggravated by dust at work. She was diagnosed with asthma 3 months after the incident.

Case 3 suffered asthma after inhalation of unusually high amounts of hydrofluoric acid vapor and NO_X. He had been working in the department for more than 6 years but had never experienced exposure to any of the acids as his main duty was welding. The symptoms occurred within minutes of him being exposed to the acid mists. He has since been relocated and his symptoms have improved.

Case 4 was exposed to isocyanates from paint. He worked as an electrician repairing electrical faults in various machines. His company was relocating to new premises. As he walked into the new plant he found someone spray- painting a machine in a room where there were no extraction fans. The spray-painter had respiratory protection and a face shield but the room was covered in a cloud of paint vapour. On that night his chest became tight and he had a cough. He consulted his doctor who gave him asthma inhalers which relieved his symptoms. He has since been on inhalers and is well controlled except for a few occasions when he is exposed to chemicals and heavy smoke. While isocyanates are known sensitizers, they are powerful irritants to the mucous membranes and the patient's clinical presentation favoured irritation rather than sensitization.

Case 5, a production process controller was exposed to unusually high levels of an irritant known as soft glide. He was opening a bucket to decant the chemical – inhaled the fumes and was admitted for chest tightness and wheezing later that day. He was then diagnosed with asthma and has been on treatment since then.

Case 6 was exposed to acetylene gas when a cylinder exploded at work. He was admitted to ICU the same day and transferred two days later to a general ward. Afterwards, he developed recurrent chest tightness, wheezing and voice hoarseness. His work involved brazing copper

and zinc metals in an electric motor manufacturing workshop where he is exposed to metal and welding fumes. He spent about two weeks per year off work due to asthma attacks.

Case 7 was a technical officer who became symptomatic (cough) 12 hours after having inhaled toxic gases whilst fixing cables in a manhole. The unidentified gas smelt like ammonia. The following night his cough worsened and he developed chest pain and chest tightness. He was given bronchodilators which help improved symptoms but he still remained with nocturnal cough and asthma was confirmed by a physician. Two co-workers also developed symptoms similar to his.

Case 8 was a man employed as a security officer, deployed to many companies monitoring video cameras and patrolling perimeters. A fire broke out in the stores on the night he was at work. Exposures included PVC fumes, magnesium, phosphorus, smoke and some gasses (possibly acetylene). There were several explosions during the fire. He spent 4 to 5 hours fighting the fire (from 09h00 – 14h20). He began feeling unwell, developed a cough and chest pain once he had finished fighting the fire. The workplace clinic transferred him to the hospital where he was admitted for 2 days. Was told he had asthma and since then, he has been on asthma medication, which relieves his symptoms.

Case 9 Her symptoms started within 24 hours of accidental exposure to an agent used for spraying pests. The agent's active ingredient is diazinon and the compound was 64% solvents. Her symptoms persisted for more than 3 months and asthma was confirmed by a pulmonologist.

Case 10 worked at a chemical manufacturer as a packer. He never suffered from any chest problems until after exposure to a mixture of phosphoric and nitric acid after a container fell. The vapours were strong but he only started experiencing chest tightness in the evening. He received medical attention at the nearby hospital. His symptoms persisted for longer than 3 months and he has to be maintained on asthma medication. Although his symptoms are milder now that he is not exposed and his lung functions are within normal limits, metacholine challenge test confirmed the presence of moderate bronchial hyper responsiveness.

Case 11 experienced chest tightness immediately after heavy exposure to cyanuric chloride, a known corrosive and irritant to mucous membranes. He consulted a doctor who prescribed "pumps" which relieve the symptoms. His symptoms persisted and were triggered by exposure to cyanuric chloride. Since he has been relocated, his asthma is controlled.

CHAPTER FOUR: DISCUSSION

This review of asthma referrals to the NIOH Occupational Medicine Clinic has highlighted causative industries and identified exposure agents implicated in cases of occupational asthma. The very wide range of industries, occupations and agents associated with these cases is suggestive of a wide-spread occupational asthma problem in the region referring cases to the Clinic. The long latency period: mean of 9.8 years and a median of seven years, was surprising. The delay in diagnosis (mean of 4.9 years and median of three years) is of concern since prompt diagnosis and removal from exposure are associated with better prognosis. Younger cases had a shorter latency period and a longer delay in diagnosis. Irritant-induced asthma is infrequently reported in the local literature, but the range of agents and jobs is possibly indicative of under-diagnosis.

Our findings are subject to several limitations. The main limitation of this study is limited representativeness of cases. Cases in this series came from a variety of industries but there are industries whose exposures are important in occupational asthma that are not within the vicinity of the NIOH e.g., platinum refining. Additionally, some cases of occupational asthma from industries with good occupational health services may have been diagnosed without being assessed at NIOH. As such, cases from these industries would rarely present to the NIOH Clinic. The NIOH Clinic is a referral clinic, so the patient population does not represent workers in the community because they first had to consult a GP or another medical practitioner who made a decision whether to refer or not. Also, the NIOH Clinic's database may have been incomplete and some cases may have been missed resulting in incomplete description of industries and agents. However, for those cases that were included in this study, there is evidence of consistency with other studies in terms of common occupational asthma causing agents.[67] Consequently, the results are still valuable in having identified common agents, occupations and industries implicated in occupational asthma in the catchment area, therefore, making it possible to target prevention.

Significant misclassification of diagnosis of occupational asthma is unlikely in this series. Although specific inhalation tests (considered as the gold standard for diagnosis of occupational asthma) were not performed in all these cases, objective evidence of asthma was verified in all cases. Cases selected were assessed by doctors experienced in occupational medicine and were all accepted by the Compensation Commissioner as occupational asthma so diagnosis was likely to be reliable in the vast majority. However, some cases did not have objective evidence of sensitization because standardized methods are lacking for many occupational agents like vanadium. Over the years, different doctors have used different criteria for confirmation of

occupational asthma diagnosis, introducing some subjectivity in case selection for the series. Some cases included here were exposed to known irritants or triggers, e.g. solvents, but did not have any other known exposure so they were accepted as cases of occupational asthma.

Although unlikely, it is possible that there are some cases of occupational asthma that were misclassified as not being occupational asthma and therefore, not included in this analysis. However, given the Clinic's interest in occupational asthma and vigorous work-up of cases, the number misclassified is likely to be small.

Being a retrospective record review, this series poses some limitations in terms of size and accuracy of data. This data set was small with limited number of variables per subject so it limited analysis. Data were not collected with this study in mind, so information from the medical records was not organized in a standardized manner, making it difficult to extract some data. For example, job descriptions were not standardized so a system had to be implemented in order to categorise jobs into standard job categories. A standardized industry list from the Compensation Fund was used as a reference for categorizing industries. [88] Although this list has helped in limiting misclassification of job and industry categories, some of the classifications were broad, e.g. "Chemical", and were poorly descriptive of the actual nature of the industry. "Chemical" does not only refer to a big chemical manufacturer but encompasses even a small enterprise whose processes are very different from the bigger enterprise.

4.1 SENSITIZER-INDUCED ASTHMA CASES

4.1.1 Causative agents, common industries and occupations

Although there are more than 300 agents known to cause occupational asthma, there are a few that are known to be common across countries. Comparing the ten most common agents in South Africa and other parts of the world with those in this series, there is consistency even though the order might not be the same.[1, 66, 81, 89, 90]

In this series, isocyanates were prominent, followed by welding fumes, vanadium and wheat. Isocyanates are still the single largest cause of occupational asthma in many countries. Isocyanates were still frequently identified in this case series. The majority of workers exposed in this series were spray painters in panel-beating shops. Thus there is little evidence that strategies for prevention and control have been implemented. Targeted intervention strategies

are probably warranted. The industry is large but generally well organized so targeted prevention is possible. Interventions to control exposure to isocyanates have been proposed by the Health and Safety Executive – UK and need to be considered in South Africa. These will include, amongst others, proper design, application and use of spray booths and rooms; and following correct working procedures.[7]

Welding of specific metals like nickel, zinc, stainless steel, particularly those with high chromium content, are established causes of occupational asthma.[91] Information on the type of welding and the metal used in welding was incomplete from the records so it was difficult to categorise welders in terms of their specific exposure agents, hence all were classified as being exposed to welding fumes. Nonetheless, even if it may have added value to identify specific agents, recommending general control measures should still be beneficial in the prevention of asthma in welders.

Vanadium is not universally accepted as a cause of occupational asthma. However, it has been reported to induce bronchial hyper responsiveness and asthma in those workers exposed to vanadium pentoxide who previously had normal lung functions.[81] Vanadium was the third most common agent in this series. All these cases arose from one smelter. This issue calls for further research in the mechanism of causality, diagnosis, tests of sensitization and intervention strategies to control exposure.

Wheat and other baking ingredients have been ranked high among asthma causing agents in most surveillance data in many countries.[58, 92, 93] It is not surprising that it was one of the four most common agents in this series. Some cases were sensitized to more than one baking ingredients. Other responsible agents were rye, alpha amylase, soya, buckwheat, etc. The majority of cases of wheat sensitization came from small-scale bakeries in supermarkets. Targeted intervention is feasible as these bakeries fall under the same employer and guidelines have been formulated.[94]

Latex has been amongst the commonest agents causing occupational asthma in South Africa in the early 2000's.[66, 95] The incidence of Latex induced occupational asthma has been decreasing since around 1997, mainly due to greater awareness of the problem and replacement of disposable natural rubber latex gloves with powder free or nitrile (latex free) gloves.[96] In this series, there were only two cases of latex allergy. This might be a true reduction in the number of latex allergy cases following substitution of latex in health care and the use of powder-free gloves as it happened in the UK.[49] On the other hand, this might be a confirmation that this

series is not representative of occupational asthma agents in South Africa; which is also confirmed by the absence of other common agents like platinum salts, resulting in platinum salt sensitivity, a common condition in the mining sector.[80] Cases of platinum salt sensitivity would have been referred to various mining occupational health services and would not be assessed at the NIOH.

Occupational asthma can be caused or associated with agents that are not found on common lists and databases. An example is cleaning agents. There is growing evidence that cleaning agents, previously not known to cause sensitizer-induced asthma, are now being recognized as established causes of asthma.[97] Thus each suspected case warrants thorough exploration of occupational, symptom and exposure histories. However, fugitive exposures have to be excluded or identified. Although there were no specific cleaning agents identified in the cases in this series, it can be assumed that they caused occupational asthma owing to work-relatedness of their condition with no evidence of pre-existing asthma. The relative constituents need to be identified to identify the sensitizing agent in these products. This is important not only in the holistic management of asthma but also in advising manufacturers of the offending agent for control purposes because cleaning is a large industry employing a growing number of employees.

Methyl Ethyl Ketone (MEK) and other solvents need special mention because they are not generally accepted as causes of sensitizer-induced occupational asthma. Some sensitizers are also irritants, e.g. isocyanates. However, these specific solvents have not been generally accepted as sensitizers. MEK is a solvent with irritant properties so the mechanism of inducing asthma could have been of long term low irritant exposure. The two cases were included in this series because: they had no previous history or diagnosis of asthma; asthma symptoms started after being exposed to MEK and when not working with MEK, asthma symptoms subsided; no other agents known to cause asthma were identified amongst workplace exposures and; the cases were accepted and awarded compensation as cases of occupational asthma. The reason for being implicated in the causation of occupational asthma in this series was based on chronological occurrence of events and evidence of work-relatedness of symptoms in previously healthy individuals. This might have caused a misclassification – cases exposed to solvents and MEK specifically may be cases of irritant induced asthma from chronic exposure to low levels of irritants, an entity not yet widely accepted, or adult- onset asthma triggered by exposure.

Unexpectedly, wood dust was not common in this series probably due to selection bias: not all industries refer their patients to the NIOH and those within the NIOH catchment area mainly consist of Engineering, Chemical, Food, Foundry and Smelter industries. The construction industry, where most cases of wood dust exposure would come from [98] although large in South Africa, is poorly served by occupational health services and it can be reasonably assumed that this large sector was under-represented in this series.

The five common industries associated with work-related asthma in developing countries are manufacturing; health care; agriculture, forestry and fishing; service work (cleaners, etc); and mining (refinery).[1] Industries that accounted for the majority of cases of occupational asthma in this series were Engineering, Chemical, Smelter, Food and Foundry sectors. Engineering is largely made up of manufacturing and the majority of cases in the Food industry category were bakers. Geographical differences account for the paucity of cases of occupational asthma from the agriculture, forestry and fishing industries in this series. These industries are not common in the NIOH catchment area.

The most common occupations were general workers, machine operators in different industries and spray painters, mainly from autobody repairers (panel beating shops). Asthma-causing agents occur in a variety of industries and can affect individuals in many occupations in these industries. Machine operators are too general a group to target prevention so each industry has to look at their labour force to check for specific exposures encountered in each group. General workers work all over the factory, as a result, can be exposed to a variety of agents. There is a need to carefully identify specific agents each group is exposed to and include them in preventive strategies for each department.

4.1.2 Age, smoking and sex differences

Age was categorised into either younger or older than 30 years. There were differences between the age groups in latency to reporting symptoms and in the time it took for cases to be diagnosed. Younger people reported symptoms sooner and it took the majority of them less than 12 months to be diagnosed. The reasons for this finding are uncertain although older people might attribute their illness to ageing and may therefore be less likely to seek medical help.

Smokers accounted for 26.7% of the cases of sensitizer-induced asthma. Cases who were current smokers at the time of exposure, developed symptoms 2 yrs earlier than non-smokers;

and it took them one year longer to be diagnosed following onset of symptoms. It is questionable as to whether the delay in diagnosis was as a result of smoking or not. Smokers might have not attributed their symptoms to workplace exposures but rather to smoking hence it took them a little bit longer to be diagnosed. The relationship between smoking and occupational asthma still needs further research because the current evidence is controversial and sometimes contradictory.[99] The recent study by Nielsen et al. suggests that the effect of smoking on occupational asthma depends on the type of allergen rather than atopy status of the individual.[100]

Although one would not expect differences in response to sensitizing agents in different sexes, there are sex differences in patterns of employment and health seeking behavior. Men tend to delay seeking health care and present to health care facilities less frequently than women.[101] In this analysis; we used sex to examine for these differences. Although not statistically significant, our data showed that men reported symptoms earlier than women. In general women would seek health care more than men. The difference in this series might be explained by the fact that women might have worked in low category occupations in industries without occupational health services, restricting their geographical and financial access to health care.

4.1.3 Latency period

Latency period in this series is taken as the time from exposure to development of symptoms. There can be a very long time between exposure and development of symptoms.[102] A study by Smith[103] describing latency period in bakers reported the mean latency period of 7.3 years with three of the 90 employees reporting symptoms in the first year of exposure. The longest latency period was 26 years. The latency period for this series was similar. It ranged from one month to 32 years with a median of seven years. Over half of the cases (80) reported developing symptoms in the first ten years of exposure with the majority thereof (48) reporting them in the first five years. Warren et al.[104] predicted a mean latency period for respiratory symptoms to be 10.3 years. Other studies[80] have reported a high proportion of cases getting symptoms within the first two years.

Latency period according to type of agent did not vary much between low molecular and high molecular weight agents. Isocyanates seemed to induce symptoms earlier than other three common agents, with cases exposed to welding fumes showing symptoms some 12 years after initial exposure.

4.1.4 Time to diagnosis

The long time from reporting development of symptoms to diagnosis is of concern in this study. It is expected that most cases will be diagnosed within 12 months after development of symptoms if annual surveillance takes place. Possible reasons for delayed diagnosis are inadequacy of surveillance in some industries, lack of access to health care, lack of awareness of hazards and their health effects on the part of the employee and the attending medical practitioner, fear of victimization by employers (hence employees hide symptoms) and general acceptance of health effects considered minor by those living in harsher conditions.

The duration of symptoms before diagnosis was the determining factor for severity of asthma in some studies. The longer the duration (more than three years), the more severe was the asthma.[105] In this series, the majority of cases were diagnosed within five years of having reported symptoms (median three years). However, it is notable that it took over ten years for 13 cases to be diagnosed. This is worrisome as the outcome is known to be unfavourable for such cases. These 13 cases came from a variety of industries, as such examining the reasons for the delay in diagnosis may not be simple, but is worthy of further research.

Of note, there were statistically significant differences between young and old people with regards to time to diagnosis. Younger people were diagnosed earlier maybe because they could have been more health conscious and presented to health care facilities earlier than older individuals.

A larger, but non-significant, proportion of smokers were diagnosed after having symptoms for longer than 12 months (85.7% versus 73.7% in non-smokers). Non-smokers were diagnosed earlier than smokers. A possible explanation might be that current smokers may not attribute their symptoms to workplace exposures, hence they delay seeking medical attention.

On average it took about 5.4 years to get diagnosed for cases exposed to LMW in comparison to 3.7 years for HMW agents. This difference is not statistically significant but might be explained by differences in distribution between these two agents. There were 105 cases exposed to low molecular weight agents versus only 26 exposed to high molecular weight agents.

Cases in the Chemical industry were two times more likely to be diagnosed earlier than other industries suggesting greater awareness of hazards and disease in this industry. Also some

chemical industries are large and thus offer comprehensive occupational health services to their employees, possibly including periodic surveillance.

Only age and the Chemical industry were significantly associated with latency period and time to diagnosis in the final models. These factors need further structured research using a bigger sample size. Campaigns to increase awareness and provide accessible occupational health services are needed.

4.2 IRRITANT-INDUCED ASTHMA

Studies of the prevalence of irritant-induced asthma have been scarce over the years particularly in developing countries. In first world countries, estimated prevalence ranged from 11 to 15% in the two sentinel projects, namely, the Surveillance of Work-related and Occupational Respiratory Disease (SWORD) in the United Kingdom and the Sentinel Event Notification System for Occupational Risks in four states in the United States.[106, 107] A similar prevalence (15%) was reported in Ontario.[108] In this series, 11 cases (7.8%) of irritant-induced asthma were exposed to various respiratory irritants in different industries. The prevalence is low but consistent with that of six percent (6%) in other studies using strict criteria and definitions for irritant-induced asthma.[109, 110] The suggestion is that irritant-induced asthma is not a common phenomenon.[111] In our context, however, lack of recognition and under-diagnosis might be plausible reasons for the low prevalence. This calls for awareness of the disease and thorough investigation of suspected cases to elicit bronchial hyper-responsiveness.

CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

In conclusion, the majority of cases (131) were as a result of exposure to sensitisers, while the remaining cases (11) were due to irritant exposure. Isocyanates and welding fumes were most common among low molecular weight agents, with wheat the commonest among high molecular weight agents. Key exposure industries were engineering and chemical. Long latency and diagnostic lag periods were present among these cases. Age was an important covariate for latency and diagnostic lag period.

Despite the limitations of a descriptive study of a selected series of patients, the data presented do provide an overview of the wide range of agents, jobs, and industries associated with occupational asthma. Data presented here can educate medical practitioners, employers, and employees about local risks and can provide basis for a surveillance system, targeted at preventing future cases.

5.2 RECOMMENDATIONS

The best intervention strategy for occupational diseases including occupational asthma is prevention. Strategies for primary and secondary prevention are discussed below.

Primary prevention: Identification of agents commonly causing occupational asthma is the first step to prevention. National surveillance schemes are useful in identifying agents, monitoring trends, setting priorities for prevention and forming the basis for further research.
Identified industries (Engineering, Chemical, Smelter, Food and Foundry sectors) need to be specifically targeted to assist them in identifying offending agents with the aim of eliminating or reducing exposure to those agents. For example, an alternative paint can be substituted for the 2-pack isocyanates paint in panel beating shops. If this is not possible, engineering controls can be instituted. These can include proper design, application and use of spray booths and rooms; and following correct working procedures. Effectiveness of engineering controls should be evaluated. Other strategies that are as effective are employee education about hazards and social habits like smoking.

Secondary prevention: The aim is to detect early signs and symptoms of asthma in workers who are potentially at risk so as to avoid further exposure. It is known that asthmatic patients who avoid exposure early on in the disease have better prognosis than those who remain exposed.[29] A structured periodic medical surveillance programme will identify those at risk of developing disease. Various tools ranging from symptom questionnaires, spirometry to immunological tests are available. These should be used in addition to elimination or reduction of exposure. Medical screening alone without exposure control is not effective in preventing disease.

Given the weakness of the labour inspectorate and poor coverage of occupational health services in South Africa, implementation of recommendations will not be easy.

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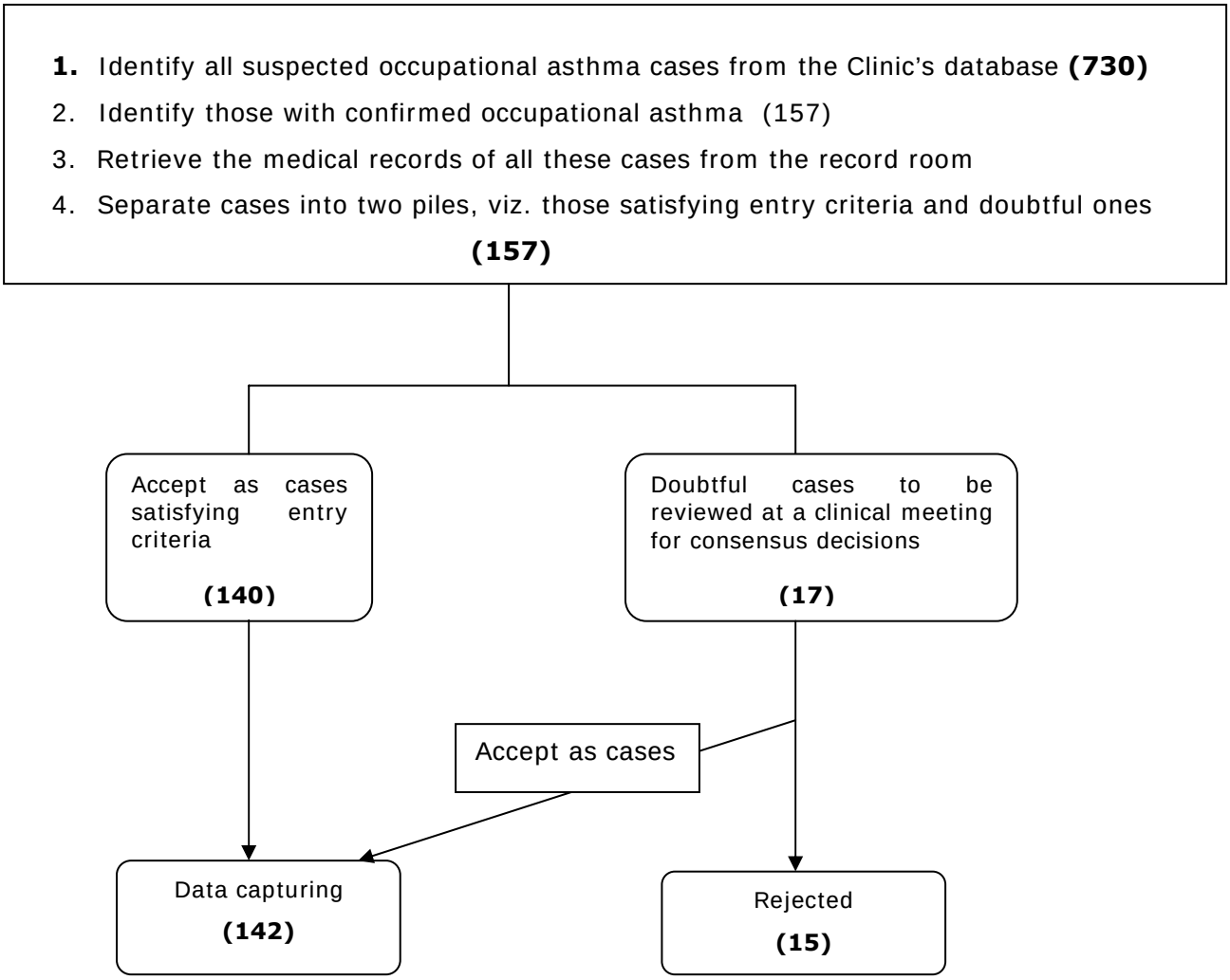
APPENDIX

APPENDIX A

Steps for data collection



APPENDIX B1

Data capture sheet

OCCUPATIONAL ASTHMA CASES : 1997 - 2007		
1. CLINIC NUMBER		☐☐☐☐☐☐☐☐☐☐
2. QUESNO		☐☐☐
4. GENDER	Male = 1 Female = 2	☐
5. AGE	Years	☐☐
6. CONAME		
7. INDTYPE		
8. JOBTYPE		
9. SYMPT TIME	Months: first exposure to onset of symptoms	☐☐☐
10. DIAG TIME	Months: first exposure to diagnosis	☐☐☐
11. SYMPT – DIAG TIME	Months: number of symptomatic months to diagnosis	☐☐☐
12. EXPAGENT	Specific name of exposure agent	
13. FREQEXP	Daily = 1 Most days = 2 1-3 days/ week = 3 Less than 1 day/ week = 4	☐
14. INTEXP	Low = 1 Medium = 2 High = 3 Medium peak = 4 High Peak = 5 Unable to classify = 6	☐
15. SMOKE HIST	Smoker = 1 Ex-Smoker = 2 Non-Smoker = 3	☐
16. PACKYR	Number of cigarettes over 20 by years of smoking	☐☐
17. DIAGNOSIS	OA = 1 IIA = 2	☐
18. DATE OF DIAGNOSIS		

APPENDIX B2

Explanation of terms on the data capturing sheet

Quesno	=	questionnaire number
Age	=	age at diagnosis (years)
Coname	=	company name
Indtype	=	type of industry where exposure occurred
Jobtype	=	type of job implicated in exposure
Sympt time (months)	=	time from first exposure to onset of asthma symptoms
Diagtime (months)	=	time from first exposure to diagnosis of asthma
Sympt –diag time	=	time in months from onset of symptoms of asthma to diagnosis
Expagent	=	type of exposure (specific name of the agent)
Freqexpo	=	Quantification of exposure within a working day or week
Intexp	=	Intensity of exposure including peak exposures (low, medium, or high constant exposure; medium or high peaks exposure)
Smoke hist more	=	smoking history (ex-smoker = has stopped smoking for than a year ago)
Packyr	=	number of cigarettes smoked per day per duration of smoking (N divided by 20, multiplied by duration of smoking in years)
Diagnosis	=	occupational asthma (OA) or irritant induced asthma (IIA)

APPENDIX C

ETHICS LETTER

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Kgalamono

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M080331**
PROJECT	Occupational asthma cases assessed at the National Institute for Occupational Health's Occupational Medicine referral clinic
INVESTIGATORS	Dr SM Kgalamono
DEPARTMENT	School of Public Health
DATE CONSIDERED	08.03.25
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.04.15 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof D Rees

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES