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Determinants of Occupational Allergic Respiratory Disease and Asthma in Spice Mill Workers



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Declaration

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

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Dedication

To my loving husband and soul mate Tjaart van der Walt

To our beautiful children Neill, Jacques, Sophia, Stefan and Regardt

To the human spirit in search of knowledge

To Creation and life making it all possible

University of Cape Town

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Abstract

Inhalation of spices has been reported to cause allergic respiratory disease and asthma in isolated reports. The aim of this study was to determine the prevalence of occupational allergy and asthma associated with airborne spice and to determine the host and environmental risk factors associated with allergic respiratory disease among spice mill workers.

A cross-sectional epidemiological study of 150 currently employed workers in a spice mill was conducted. Environmental exposure assessment entailed the collection of 62 full-shift airborne personal samples on randomly selected individuals employed in various departments of the spice mill using the NIOSH occupational exposure sampling strategy manual. The samples were analysed for inhalable particulate mass, specific spice dust allergens (garlic) and endotoxin using ELISA inhibition (antibodies from sensitised subjects) and chromogenic LAL assays. Health outcome assessment used an interviewer administered ECRHS questionnaire adapted for the spice work environment, specific IgE reactivity to common inhalant allergens (Phadiotop) and occupational allergens (garlic, chili pepper and wheat) (Phadia, ImmunoCAP), spirometry and fractional exhaled nitric oxide (FE_{NO}) using ATS/ERS criteria. Multiple linear and logistic regression analysis was conducted using Stata 8 computer software (StataCorp).

The results of the airborne samples demonstrated a wide variation in mean (geometric) current concentrations of inhalable particulate 2.06 mg/m³ (LOD-47.64), garlic allergen 0.24 µg/m³ (0.02-43.29) and endotoxin 60 EU/m³ (23-390) levels. The

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mean concentrations of dust particulate (5.78 mg/m^3) and garlic allergen ($3.71 \text{ } \mu\text{g/m}^3$) were relatively higher in the blending/sifting department, whereas endotoxin (124 EU/m^3) levels were relatively higher in the milling department. The correlation between garlic allergen and particulate dust ($r=0.70$) was much stronger than between endotoxin and particulate dust ($r=0.43$) or endotoxin and garlic allergen ($r=0.37$).

The mean age of this predominantly male (71%) workforce was 33.4 years with 46% being current smokers and 45% being atopic. The mean duration of employment in the factory was 6.9 years and 3.2 years in the current job. The prevalence of work-related upper airway symptoms due to spice dust was much higher (43%) than lower respiratory asthma-related symptoms (17%). Sensitisation to garlic (19%) was much higher than to wheat (9%) and chili pepper (6%), although these indices were highly correlated with each other ($r=0.89-0.96$). Spirometry demonstrated airway obstruction ($\text{FEV}_1 < 80\%$ predicted) in 13% of individuals and 6% with chronic obstructive pulmonary disease ($\text{FEV}_1/\text{FVC} < 70\%$). There were 4% with significant airflow reversibility (FEV_1 increase post-bronchodilator) and 8% with airway inflammation suggestive of asthma ($\text{FE}_{\text{NO}} > 50\text{ppb}$). The prevalence of allergic rhinitis due to garlic (9%) was much higher than to wheat (5%) or chili pepper (2%). A similar pattern was observed for the prevalence of probable occupational asthma, which was slightly higher due to garlic (4%) than due to wheat or chili pepper (3%).

Atopy and smoking were identified as the most important host determinants of allergic respiratory disease. In the multivariate models, work-related upper respiratory symptoms due to spice dust were strongly associated with garlic allergen exposures (OR 2.32, CI 1.06-5.05) when comparing the upper versus the lower tertile group

(>0.235 versus <0.066 $\mu\text{g}/\text{m}^3$). General work-related lower respiratory asthma symptoms were more strongly associated with higher airborne endotoxin concentration (OR 5.20, CI 1.12-24.17) for those with >59.06 versus <44.86 EU/ m^3 concentrations and garlic allergen exposures (OR 3.22, CI 1.01-10.25) for those with >0.235 versus <0.066 $\mu\text{g}/\text{m}^3$ concentrations. Furthermore, work-related lower respiratory symptoms due to spice dust were also strongly associated with sensitisation to garlic (OR 4.67, CI 1.83-11.89). A stronger association for probable asthma ($\text{FE}_{\text{NO}} > 50$ ppb) was demonstrated among workers sensitised to chili pepper (OR 23.93, CI 5.24-109.25) than to wheat (OR 6.4, CI 1.64-24.98) or garlic (OR 5, CI 1.48-16.88). A similar pattern was also observed for bronchial reversibility (FEV_1 increase post-bronchodilator) associated with chili pepper sensitisation (OR 10.92, CI 1.66-71.85). The study also demonstrated that chronic obstructive pulmonary disease (FEV_1/FVC ratio <0.7) was more strongly associated with allergic sensitisation to chili pepper (OR 15.6, CI 2.88-84.31) than due to wheat (OR 7.5, CI 1.56-36.04) or garlic (OR 4.87, CI 1.13-20.90). The associations were more pronounced among atopic workers.

In conclusion workers exposed to elevated levels (mean >2 mg/m^3) of inhalable spice dust containing allergens (garlic, chili pepper, wheat) are at an increased risk of developing work-related lower respiratory symptoms, probable asthma and chronic obstructive pulmonary disease. A stronger association was demonstrated with sensitisation to chili pepper than to garlic, despite a higher prevalence of allergic respiratory disease observed in the latter sensitised group. Atopy and smoking are important host risk factors for lower respiratory symptoms and asthma among spice mill workers.

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Glossary of Abbreviations, Symbols, Terms and Definitions

- ACGIH® = American Conference of Governmental Industrial Hygienists
- ADCRU = Allergy Diagnostic and Clinical Research Unit
- ATS = American Thoracic Society
- COPD = airflow limitation possibly indicating chronic obstructive pulmonary disease
- COSHH = Control of Substances Hazardous to Health
- DECOS = Dutch Expert Committee on Occupational Standards
- ECCS = European Community for Coal and Steel
- ECRHS = European Community Respiratory Health Survey
- ELISA = Enzyme-Linked Immunosorbent Assay
- ERS = European Respiratory Society
- EU/m³ = endotoxin units per cubic meter
- FE_{NO} = fractional concentration of exhaled nitric oxide
- FEV₁ = forced expiratory volume in one second
- FEV₁ increase post-BD = FEV₁ increase ≥12% and ≥200ml post-bronchodilator
- FVC = forced vital capacity
- HMW = high-molecular-weight
- HSE = Health and Safety Executive
- ICS = inhaled corticosteroids
- kDa = Kilodalton

- LAL = limulus amoebocyte lysate
- LEV = local extraction ventilation
- mg/m^3 = milligrams per cubic meter
- NHLS = National Health Laboratory Service
- NIOH = National Institute for Occupational Health
- NIOSH = National Institute for Occupational Safety and Health
- NO = nitric oxide
- OEL = occupational exposure limits
- OESSM = Occupational Exposure Sampling Strategy Manual
- PAS-6 = personal air-sampling head
- PBS = phosphate buffer saline
- PNOS = inhalable particulates not otherwise specified
- Post-BD = post-bronchodilator lung function test performed at least 15 minutes after the inhalation of $400\mu\text{g}$ short-acting β^2 -agonist.
- PPV = positive predictive value
- PR = pathogenesis-related
- RAST = radioallergosorbent test
- SDS-PAGE = sodium dodecyl sulphate polyacrylamide gel-electrophoresis
- SORDSA = Surveillance of Work-related and Occupational Respiratory Diseases
- SQR = Simultaneous quantile regression
- TID = total inhalable dust
- TLC = total lung capacity
- $\mu\text{g/m}^3$ = micrograms per cubic meter

- WRURS = work-related upper respiratory symptoms defined as the presence of symptoms of work-related nasal and ocular irritation i.e. sneezy/itchy/runny nose or red/itchy/watery eyes.
- WRURS due to spice = work-related upper respiratory symptoms due to spice dust defined as the presence of sneezy/ itchy/runny nose and or red/itchy/watery eyes related to spices at work.
- WRLRS = work-related lower respiratory symptoms defined as the presence of symptoms of work-related chest tightness or wheeze.
- WRLRS due to spice = work-related lower respiratory symptoms due to spice dust defined as the presence of symptoms of chest tightness and wheeze caused by spice as reported by the worker.

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Chapter 1

1.1 Introduction and background

Reports of a number of workers with work-related allergy and asthma from a spice mill after prolonged exposure to high levels ($>10\text{mg}/\text{m}^3$) of inhalable spice dust, prompted detailed investigation of three index cases. Detailed analysis of their immune responses to an extensive range of spices to identify the putative allergens responsible for the allergic symptoms following inhalation of spice dust was conducted. Although garlic powder dust was identified as the main spice reported by the workers to be causing their symptoms, other spice blends containing onion, cayenne and chili pepper as well as soya were implicated. This index case study demonstrated IgE reactivity to multiple spice allergens in workers exposed to high levels of inhalable spice dust. Further investigation of sera and immunoblotting demonstrated a 50kDa cross-reactive allergen in garlic and onion, and allergens of approximately 40kDa and 52kDa in chili pepper. The study also found that dry powdered garlic and onion in the factory demonstrated greater IgE binding than the raw form commonly handled in the domestic environment. The study also demonstrated that atopy and polysensitisation to various plant profilins, suggesting pollen-food syndrome, represent additional risk factors for sensitiser-induced work-related asthma in spice mill workers (Appendix A).

A closer look at taxonomical relationships revealed that allergic sensitisation to spice families Alliaceae (*Liliatae*) and Solanaceae, Apiaceae (*Magnoliatae*) was prominent in all three workers. These spice families are surprisingly different and botanically

unrelated (Figure 1). In comparison to ingested food allergy very different patterns have been observed, in that spice family Alliaceae is less prominent in causing sensitisation whereas spice families Apiaceae and Solanaceae are responsible for most of the hypersensitivity reactions (Schöll and Jensen-Jarolim, 2004). These differences therefore need further exploration in evaluating occupational allergic disease associated with inhalation of spice dust.

Limited information is available on occupational allergy to spices in Southern African workplaces. Occupational asthma to onion (Mansoor and Ramafi, 2000) and an upper respiratory symptom survey among workers occupationally exposed to spices are the only two studies reported (Goring, 2003). Most of the studies on occupational asthma caused by inhalation of garlic, have investigated IgE reactivity patterns only to the specific spice, (Henson, 1940; Falleroni et al., 1981; Lybarger et al., 1982; Couturier and Bousquet, 1982; Seuri et al., 1993; Shao-Hsuan et al., 2004) whereas in spice mills, spice workers have concurrent exposures to multiple spices during work activities, which may impact on their symptoms. An added complexity in identifying putative allergens in spice mill workers is the wide variation of spice blends produced that is dependent on local availability, geographic tradition and recipes of popular manufacturers.

It is within this context that a detailed epidemiological investigation of spice mill workers, which focuses on their exposures, patterns of sensitisation, prevalence of upper and lower airway symptoms, as well as risk factors for these clinical endpoints, is needed.

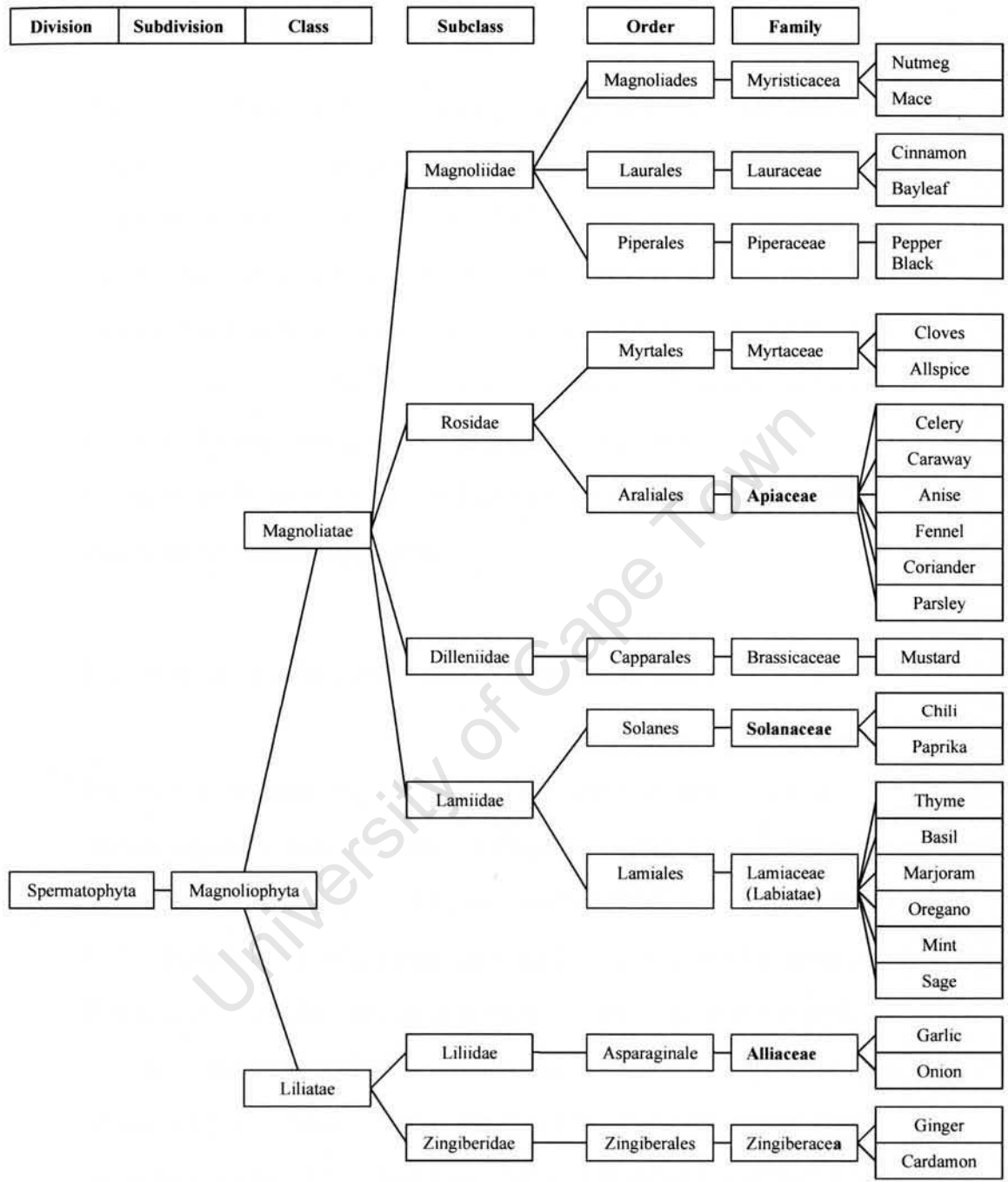


Figure 1: Taxonomical Relationships in the Family of Spices (Schöll and Jensen-Jarolim, 2004)

1.2 Literature Review

This review focuses on work-related allergy and respiratory disease associated with spice milling, processing and packing of spice products. To identify relevant manuscripts, PUBMED, MEDLINE and EBSCO searches were undertaken for studies on occupational spice allergy and respiratory disease since 1940. The keywords used included epidemiology, asthma, allergy, respiratory, immunology, spice, garlic, chili, wheat, endotoxin, work-related, workplace, occupational. Only selected publications were used after evaluation, as this review focuses on occupational allergy and respiratory health effects associated with inhalable spice dust among spice workers and not ingestion-related food allergy.

1.2.1 Food processing industry and allergic disease

The food industry employs a large proportion of workers exposed to potential allergens capable of causing occupational allergies and asthma (Jeebhay, 2002). Among consumers reporting food allergies, that affect 2% of the adult population in the industrialised world, spice allergy represents 2% of such cases (Muhlemann and Wüthrich, 1991). The total number of employees exposed to spice dust in South Africa remains unclear, but the food manufacturing and processing industry in South Africa employs over 180,000 workers who were involved in a broad spectrum of occupations (Jeebhay, 2002). Workers are employed in various sectors involved in processing of meat, fish, fruit, vegetables, oils and fats; dairy products; grain mill products, starches and prepared animal feeds; and beverages. Materials processed include both raw products (plant/vegetable, animal or microbial origin) and chemicals

for food preservation, flavouring, packaging and labelling. These biological and chemical materials are known to contain sensitising agents capable of causing occupational allergies among high-risk working populations. Food processing activities such as thermal denaturation, acidification and fermentation may destroy allergens, cause conformational changes or result in the formation of new sensitising epitopes which may increase the allergenicity of the protein.

In the occupational setting, allergic constituents of food products enter the body either through inhalation or dermal contact, resulting in adverse reactions on an irritant or allergic basis. Gill *et al.* outline the allergic diseases commonly encountered in the food industry, which include occupational asthma, rhinitis, conjunctivitis, dermatitis, and hypersensitivity pneumonitis (Gill *et al.*, 2002). Occupational asthma represents between 3% and 20% of all asthma cases and is the most common form of occupational lung disease. Occupational skin diseases may represent between 10% and 15% of all occupational diseases and have significant economic impact. Data from a voluntary South African SORDSA surveillance program described 44 cases of occupational asthma (14.4%) reported in food handlers (October 1996 to June 2002) (Esterhuizen and Rees, 2002). The majority of cases were due to flour and grain (80%), and baking (27%) and milling (18%) industries. The true burden of occupational diseases in milling, blending and packaging processes of spices in South Africa is still unknown.

1.2.2 Spice industry working populations at risk and environmental exposures

Occupational exposure to spice allergens occurs mainly in spice milling, food industry and herb processing plants. During spice milling, blending/sifting, weighing, scooping and packing activities visible dust is generated that might lead to high exposures that are inhaled by exposed workers. Limited studies are available on exposure assessment in the spice milling industry and there is great variability of exposure within and among various jobs during the handling and milling processes of spices.

In a study of spice grinders in Singapore, spice dust levels ranged from 0.03 to 0.82 mg/m³, with a mean value of 0.15 mg/m³ (Chan et al., 1990). Slightly higher levels of airborne dust (1-2 mg/m³) have been reported in packaging of buckwheat in a company that imported, prepared and distributed plant products used in spices and “health foods” (Göhte et al., 1983). Studies of inhalable dust concentrations in the work areas of Croatian spice factory workers ranged between 0.5-10.1 mg/m³ (mean 2.9 mg/m³) (Kanceljak-Macan et al., 2004). Polish studies of workers processing herbs (nettle, caraway, birch, celandine, marjoram, mint, peppermint, sage, St. John’s wort, calamus, yarrow) have reported very high levels of dust and endotoxin associated with bacterial and fungal contamination (Dutkiewicz et al., 2001). The concentrations of airborne dust ranged between 3.2-946.0 mg/m³ (median 18.1 mg/m³), exceeding the Polish occupational exposure limit (OEL) value of 4 mg/m³. The airborne endotoxin concentrations in this study ranged between 0.2-2681.0 × 10⁴ EU/m³ (median 16.0 × 10⁴ EU/m³). During peppermint and chamomile herb processing, high median concentrations of airborne microorganisms, inhalable dust

(peppermint 552.3 mg/m³, chamomile 12.3 mg/m³) and endotoxin levels (peppermint 57.3 × 10⁴ EU/m³, chamomile 0.96 × 10⁴ EU/m³) have also been reported (Skórska et al., 2005).

A number of factors influence the manifestation of allergic disease in relation to the environmental exposures. These include dose, duration and route of exposure, biochemical properties (e.g. stimulate histamine release), physical properties (e.g. alteration of the protein structure due to processing), immunological properties (e.g. allergenic potency and cross-reactivity of different spice antigens) and industrial hygiene and engineering practices (Lehrer and O'Neil, 1992). However, the level of exposure is probably the most important determinant of IgE-mediated sensitisation to occupational agents and the development of work-related allergic disease outcomes among exposed workers (Moscatto et al., 2008). On the other hand, very low levels are needed to elicit allergic symptoms ranging from skin reactions due to skin contact, food-associated symptoms after ingestion and/or asthma after inhaling spice dust (Schöll and Jensen-Jarolim, 2004).

1.2.3 Constituents of dust in spice mills

Organic dust derived in a spice mill contains pure spice or blends from various different botanical families (Figure 1). Since spices are derived from plants, they have allergenic potential due to the bioactive ingredients present in processed vegetable dusts (Schöll and Jensen-Jarolim, 2004). The majority of allergens in the food industry are of high-molecular-weight (HMW) e.g. flour, soybean dust, vegetable gums, animal proteins (Gill et al., 2002), typically in the 5-70kDa range that can

provoke a specific IgE mediated response in exposed workers (Heederik et al., 1999). Spice dust allergens are potentially high-molecular-weight sensitisers (Schöll and Jensen-Jarolim, 2004). However, irritant reactions in addition to allergic responses in workers handling spices have also been reported (Zuskin et al., 1988a). Cereal flour containing wheat proteins (added to) in spice blends are well-known high-molecular-weight sensitisers (Heederik et al., 1999). Aside from cereal flours (wheat, rye, barley, rice flour, cereal malt flour), non-cereal flours (soybean, buckwheat, lecithin from soybean) are also potential allergens as these ingredients have been reported to be potential occupational allergens causing allergy and asthma in bakers (Baatjies and Jeebhay, 2002). These well-known high-molecular-weight sensitisers may very well be added to spice mixtures and have the potential to cause allergic respiratory disease.

Additives to spices such as preservatives are known for their potential allergenicity. Sulphur dioxide is used extensively in the food industry for the preservation of food (Steinman et al., 1993). Preservatives (sodium benzoate, potassium-metabisulphite), added ingredients to spice recipes, could potentially become “inhalant” allergens when aerosolised during spice blending processes (Van der Walt et al., 2010). Natural red dyes are also used as colorants in spice production and hypersensitivity reactions have been reported to carmine proteins, known high-molecular-weight proteins from cochineal extract (Acero et al., 1988).

Dust generated during herb processing (peppermint, sage, marjoram, mint, caraway) has been shown to be contaminated with microorganisms (fungi, bacteria) as well as endotoxins (Dutkiewicz et al., 2001). Mycotoxins such as ochratoxin can also

contaminate spices, coffee, cocoa beans and foods, and may pose a health risk for workers in the spice industry (Iavicoli et al., 2002).

Aside from milling individual spices, spice plants package various spice blends that consist of many different mixtures of spices. Table 1 outlines the composition of some common blends used in a spice mill. It is evident that garlic powder, wheat/maize and various types of dried hot peppers (chili pepper, paprika rosen, cayenne pepper) appear as essential ingredients of these different recipes.

Table 1: Blends composed of a variety of spices according to a local manufacturer's recipe

Spice blends	Composed of
Cajun seasoning	black pepper, chili powder, garlic powder, nutmeg, onion powder, parsley flakes, cayenne (red pepper), salt.
Season-all	black pepper, celery seed, chili pepper, coriander, garlic powder, nutmeg, onion, paprika, salt.
Lemon and pepper	black pepper, celery seed, citric acid, cornstarch, garlic powder, lemon oil, onion, salt, sugar.
BBQ marinade	parsley, garlic powder, garlic liquid, onion powder, mustard, thyme, pepper cayenne, pepper black, paprika oleo, paprika rosen, tomato powder, cumin, sugar brown, dextrose, salt, guar gum, sodium benzoate.
Fleischwurst seasoning	soya flour, maize starch, paprika rosen, cloves, coriander, ginger, nutmeg, pepper white, celery flavour, black pepper, dextrose, sugar white, salt, ascorbic acid, lecithin, sodium nitrate, erythrosine, sodium carbonate.

1.2.4 Biochemical/immunological properties of spice allergens

Spices are the most attractive ingredients to confer an authentic taste to food.

However, besides their undoubtedly attractive properties, spice dust being an organic dust has various biological effects (Figure 2) that are mediated through various pathophysiological mechanisms.

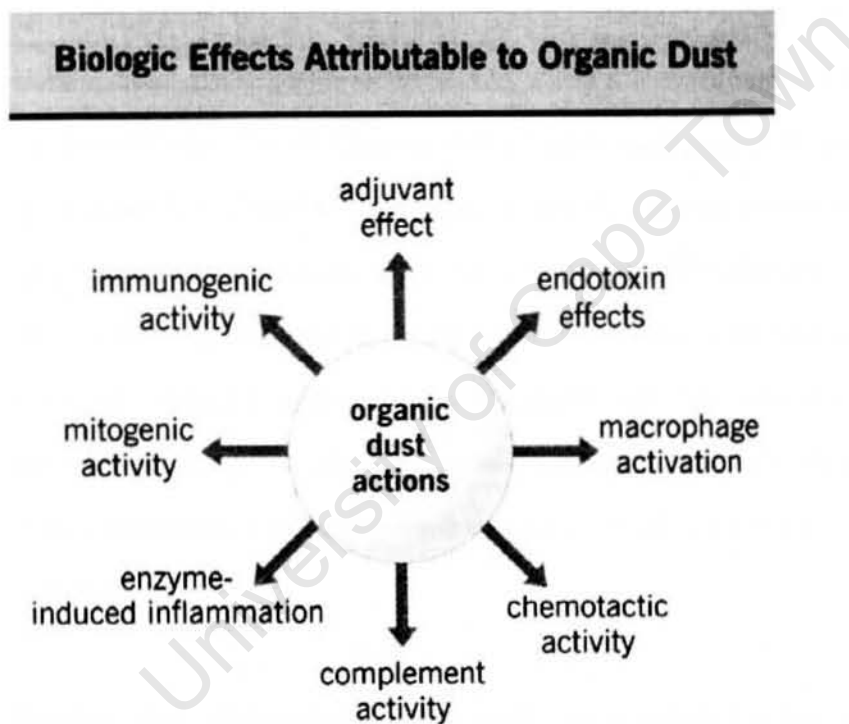


Figure 2 Biological effects attributable to organic dust (Salvaggio and Hendrick, 2001)

It is well known that aside from ingestion-related food allergy, various spices can also cause inhalant allergies through its immunogenic activity, which is commonly IgE-mediated (Schöll and Jensen-Jarolim, 2004).

Garlic (*Allium sativum*) belongs to the Alliaceae family (formerly Liliaceae), together with other members such as, onion, leek, shallot and asparagus (Figure 1). Patients with asthma induced by garlic dust have been shown to display immunologic evidence of cross allergenicity with other related members of the Liliaceae family (Lybarger et al., 1982; Anibarro et al., 1997). Several garlic protein allergens have been identified using IgE immunoblotting techniques. In individuals with occupational asthma due to garlic two major protein bands have been demonstrated at approximately 12kDa and 54kDa in garlic sensitised workers (Anibarro et al., 1997). The latter proved to be the major IgE-binding protein and shared similar allergenic epitopes with onion. Several Liliaceae share allergenic components with garlic, demonstrated by SDS-PAGE immunoblotting, when IgE-binding proteins of 12kDa were found in young garlic, garlic, onion and leek extracts (Pérez-Pimiento et al., 1999). Alliin lyase, a 56kDa IgE-binding protein, has recently been identified as a major garlic allergen in a group of Taiwanese patients aged 7-48 years with garlic allergy (Shao-Hsuan et al., 2004). This protein is widely distributed in other *Allium* species, namely leek, shallot, onion, and has been described as a potentially new cross-reactive allergen.

Homology exists among allergens due to protein sequence identity conservation, structural/conformational similarities and the frequent occurrence of certain biochemical functions among allergens (Radauer et al., 2008). Evidence of cross-reactivity between onion and garlic has also been shown in previous case reports of occupational asthma. Two main IgE-binding proteins with molecular weights of 55 and 35kDa were revealed in extracts of fresh garlic and onion, and only the 35kDa protein showed strong IgE binding with sera from a worker diagnosed with

occupational asthma due to onion (Mansoor and Ramafi, 2000). In another case report, IgE immunoblotting showed very strong bands at 14 and 40kDa with garlic extract in a worker diagnosed with occupational rhino-conjunctivitis due to garlic and onion dust exposure (Jiménez-Timon et al., 2002). Characterization of ground green and black pepper (*Piperaceaea*) and paprika (*Solanaceaea*) allergens by N-terminal amino sequence analysis proved that a 28kDa allergen identified for pepper showed 70% similarity to and 58% identity with the N-terminus of wheat germin protein (Leitner et al., 1998; Jensen-Jarolim et al., 1998b). These studies also identified a 23kDa paprika allergen that showed 100% identity with the N-terminus of tomato protein called pathogenesis-related protein PR23. Moreover, cross-reacting allergenic molecules in the range of 60kDa were also found to be responsible for type 1 allergy to anise, fennel, coriander or cumin, members of the Apiaceae family (Jensen-Jarolim et al., 1997).

Evidence for adjuvant effects of spice dust have also been suggested. Schöll *et al.* have suggested that the hotter spices are, as is the case with chili, the more likely they could act as adjuvants for sensitisation by promoting the transport of other molecules below a molecular mass of 70kDa (Jensen-Jarolim et al., 1998a; Schöll and Jensen-Jarolim, 2004). This molecular size corresponds to the size of molecules that are relevant for sensitisation and IgE binding in spice allergy. This adjuvant effect might also contribute to multiple sensitisations to airborne spice allergens as has been demonstrated in our previous studies (Van der Walt et al., 2010). It has also been shown that flour dust from bakeries and flour dust extract are strongly pro-inflammatory and can cause non-allergic airway inflammation and can enhance allergen-mediated airway inflammation (Marraccini et al., 2008).

Aside from innate biological properties, spices, when processed, may also change their ability to cause adverse health effects. Hot spices, paprika and chili pepper (*Solanaceae*), are routinely processed by drying and grinding (Schöll and Jensen-Jarolim, 2004). This procedure destroys Bet v 1 homologues as well as profilins mainly for paprika (Leitner et al., 1998) derived from dried bell-pepper fruits (Ebner et al., 1998). The higher-molecular-weight molecules of spices of the *Solanaceae* as well as the *Apiaceae* families expressing cross-reactive carbohydrate determinants (Bauer et al., 1996; Jensen-Jarolim et al., 2002) seem to be more resistant to food processing including grinding, roasting and cooking, and retain the potential to induce clinical symptoms (Leitner et al., 1998; Ballmer-Weber et al., 2002). Depending on the extent and type of processing of the raw spice, enhancement of the IgE binding capability of the allergen is also possible, as has been demonstrated for garlic and onion powder processed in the dry form in spice mill workers with work-related asthma (Van der Walt et al., 2010).

Aside from the immunogenic- and inflammatory-related effects, evidence for irritative mechanisms has also been reported. Work-related respiratory symptoms of an irritant nature have been reported in epidemiological studies of chili grinders (Uragoda, 1967, 1983). In animal studies, different spices (chili pepper, paprika, caraway, coriander leaves, coriander seeds, cinnamon, ginger, onion, curry and parsley) have demonstrated a dose-related contractile response of isolated guinea pig tracheal smooth muscle. This finding suggests that the dusty conditions in spice factories represent a highly efficient direct bronchoconstrictor challenge of the respiratory tract (Zuskin et al., 1988a). Lundberg *et al.* (1983) found that the substance P and capsaicin

(an active ingredient in chili and paprika) induced a dose-dependent contraction of human segmental bronchi *in vitro*.

1.2.5 Pollinosis and the food-pollen syndrome in spice allergy

Individuals with pollinosis often display sensitisation to various plant-derived foods (class 2 food allergies). These reactions are the result of IgE cross-reactivity to profilins and lipid transfer proteins, but may also be due to high-molecular-weight glycoproteins (Egger et al., 2006). Spice allergy has also been commonly described in association with sensitisation to common pollen inhalants (Schöll and Jensen-Jarolim, 2004). The closer the plant producing the pollen is related to the spice, the more likely cross-reactions may occur. IgE cross reactivity is due to the presence of conserved homologues in different plants (Ebner et al., 1998). Mugwort and birch pollen sensitisation represent a high risk factor for progression to spice allergy (Jensen-Jarolim et al., 1997).

Profilin and a homologue of the major birch pollen allergen Bet v 1 seem to be responsible for much of the cross-reactivity (Bauer et al., 1996; Ebner et al., 1998) and have been detected in certain strains of bell peppers (*Capsicum annuum*) as well as for the Apiaceae family of spices (Jensen-Jarolim et al., 1998b; Ebner et al., 1998). Dried Apiaceae spices like anise, fennel, coriander or cumin contain genetically intact Bet v 1 and profilin homologues and may, besides other high molecular weight allergenic agents, be responsible for the type I allergic responses (Jensen-Jarolim et al., 1997). This may be an important cause of cross-reactions within the Apiaceae family, as well as to pollen (Stäger et al., 1991).

Clinical pollen-food syndromes such as the mugwort-mustard-allergy, celery-mugwort-spice-allergy and the celery-birch-mugwort-spice syndrome have been previously described (Bauer et al., 1996, Figueroa et al., 2005). Patients with food allergies specifically to Liliaceae (garlic, onion, leek) have also been found to have celery-mugwort-spice syndrome (Moneret-Vautrin et al., 2002). Birch tree (*Betula verrucosa*) profilin Bet v 2 and mugwort (*Artemisia vulgaris*) profilin Art v 4 have been identified as significant contributors to allergic reactions to pollen and plant-derived food within the celery-birch-mugwort association due to cross-reaction with celery profilin Api g 4 (Vallier et al., 1988; Scheurer et al., 2000).

Leitner *et al.* (1998) however, investigated allergens originating from pepper (*Piperaceae*) and paprika (*Solanaceae*) and showed that IgE cross-reactivity in the celery-birch-mugwort-spice syndrome to spices other than Apiaceae (carrot, caraway seeds, parsley, fennel seeds, coriander seeds, aniseed) is not exclusively caused by Bet v 1 homologues and/or profilins. The celery-mugwort or celery-birch-mugwort association comprises additional botanical families such as Solanaceae (paprika), Piperaceae (pepper) and Liliaceae (garlic, onion) (Moneret-Vautrin et al., 2002).

The number of allergen sources involved, the nature of the allergens and the influencing factors render the celery-birch-mugwort-spice syndrome a clinical feature of high complexity. Interestingly, cross-reactivity of grass pollens (*Phleum pratense*) with garlic allergens was confirmed in previous immunoblotting inhibition studies (Anibarro et al., 1997). Sensitisation to grass pollens (*Phleum pratense*) might therefore also be a potential risk factor for the development of garlic allergy.

Furthermore, immunoblotting confirmed cross-reactivity of mugwort, paprika, short ragweed and black pepper with unique allergens (67 to 75kDa) in fennel seed in a sensitised (fennel) atopic spice worker (Schwartz et al., 1997). A significant degree of cross-reactivity was also demonstrated between saffron and *Lolium*, *Salsola*, or *Olea* pollens by RAST inhibition studies (Feo et al., 1997). It can be concluded that allergy to spices rarely represents an autonomous sensitisation, but is rather a consequence of pollen allergy on the basis of immunologic cross-reactivity (Ebner et al., 1998).

1.2.6 Health effects of spices

The bioactive ingredients in spices have the potential of inducing symptoms ranging from mild local to severe systemic allergic reactions (Schöll and Jensen-Jarolim, 2004). Workers in the spice-related industry are exposed to a variety of different respiratory sensitisers that may cause sensitisation through inhalation or skin contact. Inhalation of spice dust has the potential to cause respiratory allergies such as rhinoconjunctivitis, asthma, and allergic alveolitis, contact dermatitis and occasionally anaphylaxis (Schöll and Jensen-Jarolim, 2004). Exposure to high-molecular-weight allergens such as spices may result in IgE-mediated rhinitis, conjunctivitis and asthma. Studies have also shown that symptoms of occupational rhinitis are more often reported to precede occupational asthma in the case of high-molecular-weight (HMW) compared to low-molecular-weight agents (Malo et al., 1997).

The food industry accounts for the largest number of cases with occupational rhinitis (Meggs, 1994), and the prevalence of occupational allergic rhinitis has been reported to be between 3% and 60% (Gill et al., 2002) depending on the exposure environment

and the level of exposure (Moscatto et al., 2008). The prevalence of rhino-conjunctivitis in subjects with occupational asthma was found to be 76-92% (Malo et al., 1997). Occupational rhino-conjunctivitis has been previously described for a spice worker handling garlic and onion powder dusts by nasal challenge test (Jiménez-Timon et al., 2002) and usually precedes the development of occupational asthma (Seuri et al., 1993). Fennel seed and saffron (pollen and stamen proteins) have also been associated with IgE mediated sensitisation in spice workers and the subsequent development of occupational allergic rhino-conjunctivitis and asthma (Schwartz et al., 1997; Feo et al., 1997). In a study of workers preparing and distributing plant products, buckwheat used in spices and “health foods”, a high prevalence of work-related symptoms of rhinitis (39%), asthma (21%) and conjunctivitis (18%) were recorded and a strong correlation was observed between those with positive allergy tests (28%) and work-related symptoms (Göhte et al., 1983). A similar high prevalence of asthma (22.5%) has been reported in Sri Lankan workers processing cinnamon (Uragoda, 1984).

Various studies have also reported symptoms of upper and lower airway irritation in relation to spice dust. A high prevalence (49.2%) of upper respiratory tract symptoms of irritation (sneezing and runny nose) has been reported for spice grinders in Singapore (Chan et al., 1990). Respiratory symptoms of irritant nature have also been documented in Sri Lanka for workers exposed to spice dust containing cinnamon (88%), cloves (76%) and pepper (44%) (Uragoda, 1992), as well as for chili grinders (95%) (Uragoda, 1967). Inhalation of capsaicin however, does cause dose-dependent coughing in subjects with and without asthma (Collier et al., 1984). Among capsicum-

exposed workers the reported prevalence of cough (59%) was more than double the prevalence in the non-exposed controls (21%) (Blanc et al., 1991).

Studies of lower respiratory symptoms and lung function associated with organic dust exposures in the food processing industry have consistently demonstrated a higher prevalence of both acute and chronic respiratory symptoms (Zuskin et al., 2000). Among exposed workers a high prevalence of chronic cough (40%), acute dry cough (58.7%) has been reported. Pulmonary function impairment manifesting as across-shift FEV₁ (-9.9%) and FVC (-3.7%) changes and particularly marked small airways changes FEF₂₅ (-26.7%) and FEF₅₀ (-21.6%) alluding to asthma have also been reported. However, studies of chili grinders show that no statistically significant across-shift change in lung function nor any significant difference in pre-shift measures was recorded for chili grinders in Sri Lanka when compared to the controls (Lankatilake and Uragoda, 1993).

Occupational asthma has been reported to a range of spices including cinnamon, paprika, mace, coriander, aniseed, garlic and onion (Uragoda, 1984; Sastre et al., 1996; Fraj et al., 1996; Mansoor and Ramafi, 2000). Garlic (*Allium sativum*) belongs to the Alliaceae family (formerly Liliaceae), with the first report of garlic-induced asthma dating back to 1940, when Henson described an atopic foreman with ragweed pollinosis whose asthmatic symptoms disappeared after the garlic “powder” was replaced with “kernels” (Henson, 1940). Inhalation-related garlic allergy has since been reported in different occupational settings including food preparation and catering, sausage making, harvesting and storing of garlic bulbs, spice manufacturing,

as well as packing and selling of spices (Falleroni et al., 1981; Lybarger et al., 1982; Seuri et al., 1993; Anibarro et al., 1997).

Grinding of dried red chilies into a fine powder has been implicated as the cause of respiratory symptoms particularly in environments heavily contaminated with chili powder (Uragoda, 1967). Occupational exposure to paprika dust has been associated with the development of hypersensitivity pneumonitis “paprika splitter’s lung” (Fink, 1973). Processing of chili does not involve splitting the fruits, and furthermore, chili workers are not exposed to *Mucor stolonifer* as in the case of paprika splitters. Although chili and paprika both belong to the genus *Capsicum*, and contain the pungent capsaicin in the fruits, fibrosing alveolitis has not been demonstrated for chili workers (Uragoda, 1983).

1.2.7 Risk factors for allergic sensitisation and the development of asthma

Host factors play an important role in disease development, since only a limited number of presumably uniformly exposed workers develop occupational disease. Host factors include atopy, prior allergic sensitisation to the specific occupational allergen, occupational rhino-conjunctivitis, airway hyperresponsiveness, genetic factors and smoking (Tarlo et al., 2009). Approximately 5% of workers exposed to sensitising agents develop occupational asthma (Gill et al., 2002). Therefore, host factors are likely to affect an individual’s risk of developing occupational asthma.

Atopy is an important risk factor for IgE mediated reactivity to high-molecular-weight allergens (Moscato et al., 2008), but less relevant for non-IgE-mediated occupational asthma (Gill et al., 2002). Although atopic individuals are at an increased risk of asthma due to high-molecular-weight occupational agents, atopy itself is a weak predictor of sensitisation and development of occupational asthma (Jeebhay and Quirce, 2007). Atopy and simultaneous sensitisation to various plant profilins may pose additional risk factors for sensitisation to class 2 allergens and the development of occupational asthma in spice mill workers (Van der Walt et al., 2010).

Occupational rhinitis is associated with an increased risk of asthma, although the proportion of subjects with occupational rhinitis who will develop occupational asthma remains unknown (Moscato et al., 2008). Malo *et al.* (1997) suggested that in the case of high-molecular-weight agents (HMW), the appearance of rhinoconjunctivitis in a sensitised individual might be a marker of the likelihood of developing occupational asthma. Ocular-nasal symptoms often precede and coexist with occupational asthma symptoms in the case of high-molecular-weight agents (HMW) agents (Moscato et al., 2008). The prevention of work-related rhinitis may also provide an excellent opportunity to prevent the development of occupational asthma (Moscato et al., 2008).

The relationships between smoking and occupational asthma, occupational rhinitis and occupational sensitisation are complex, controversial and contradictory. Data from an in-depth review on various studies done, from 1970 to 2005, for a wide range of occupations, from laboratory, farm, brewery and hospital workers, to bakers, printers, cleaners and others showed surprisingly little to support the view that the risk

of occupational asthma is increased in workers who are smokers (Siracusa et al., 2006). A recent study though, showed that smoking might pose an additional risk factor for allergic sensitisation to wheat flour or enzymes in atopic workers (Harris-Roberts et al., 2009). Very little is known about the association between smoking and occupational sensitisation and asthma to spice dust. However, studies by Zuskin *et al.* suggest that aside from dust exposures, smoking is independently related to across-shift respiratory symptoms and decline in lung function in workers exposed to spice dust (Zuskin et al., 2000).

Furthermore, environmental factors such as exposure concentration and duration are important determinants of occupational allergy and asthma to spices. The interaction between exposure to occupational allergens and other co-factors in the environment, such as endotoxin, are also important risk factors in the development of sensitisation and asthma (Jones, 2008). The relationship between endotoxin exposure and health effects is still controversial due to the paradoxical nature of the health effects observed (Radon, 2006). Some studies have demonstrated protective response for developing asthma, while others show priming of the allergic response and an exacerbation of asthma (Singh et al., 2010). Detailed exposure-response relationships in spice mill workers, in relation to specific spice allergen exposure concentrations have not been conducted and needs to be explored further.

1.2.8 Conclusion

In conclusion, this review has illustrated that spice dust is not a biologically inert dust as it has been associated with various disease endpoints including occupational allergy

and asthma. However, the prevalence and determinants of occupational respiratory allergy and asthma to airborne spices among spice mill workers in South Africa needs further investigation as this review has highlighted some important gaps in the literature that could be addressed through such a study.

University of Cape Town

1.3 Aim and Objectives

Aim

To determine the prevalence of occupational spice allergy and asthma and the risk factors associated with allergic respiratory disease among spice mill workers.

Objectives

1. To document environmental airborne exposures of workers involved in spice milling and packaging processes of spice product through measurement of inhalable particulate dust, garlic allergen and endotoxin concentrations using personal time-integrated environmental sampling of workers.
2. To determine the prevalence of IgE-mediated sensitisation and allergic respiratory disease endpoints such as rhino-conjunctivitis and asthma associated with spice allergens through measurement of allergic sensitisation, airway obstruction and inflammation.
3. To document the relationship between exposure to spice dust, sensitisation and allergic respiratory disease endpoints.
4. To investigate which of the following are risk factors for sensitisation and allergic respiratory disease associated with spice processing:

- Host-related: age, gender, smoking status, atopy, current history of ocular-nasal symptoms
- Work-related: level of airborne exposure to spice particulate dust, garlic allergen and endotoxin concentrations

University of Cape Town

Chapter 2

Methodology

2.1 Study design and population

A cross-sectional study of all currently employed workers in a spice mill was conducted. All workers employed in the production area of the spice mill as well as staff working in the stores/distribution department, administration and the laboratory were included. The workforce is reasonably sized and stable with 160 permanent staff currently employed at the spice mill. Based on past experience with conducting studies among similar populations in the Western Cape and given the enthusiastic support of stakeholders for this proposed study, we expected participation rates to be close to 100 percent.

2.2 Environmental exposure assessment

Exposure assessment was conducted using a combination of personal exposure time-integrated measurements and work history information to develop several exposure metrics for analysis. Personal ambient inhalable dust particulate, garlic allergen and endotoxin concentration exposure levels of the spice mill workers were measured, analysed and categorised.

2.2.1 Work processes in spice mill

The production area of the spice mill was a general area where all the processing activities such as blending and packing of spice product were conducted except for milling, which occurred in a separate area (Figure 3). Dry materials such as peppercorns, coriander, paprika and chili peppers (*Capsicum annuum*) were crushed and grounded in the milling area. Only hot dried peppers as opposed to fresh bell peppers were used during the milling of spice. Garlic was also used in a dried form as flakes, powder or granules during the blending of spice in the spice mill. An independent supplier manufactured the garlic product used in the spice mill. A steam heat process at 65°C lasting 5 hours produced the garlic flakes during the manufacturing process. In the spice mill all the spices were fed through hoppers and blended together to produce different recipes. The raw materials, blended together, were released through a discharge chute into containers/bins. Containers were taken up the packing gantry by use of an automatic crane and fed into packing hoppers, at the top gantry, then into packing machines. Different types of automated packing machines (sachet machine) packaged the final spice product or spices were hand packed. The sealed packages were placed in containers earmarked for retail delivery (Appendix M).

2.2.2 Sampling strategy

The spice mill was stratified into high, medium and low/no exposure areas by visual inspection of the dust generating work process activities and information from previous dust survey measurements. High exposure to spice dust was classified as blending/sifting, packing and weighing work areas. Medium exposure involved milling and stock control stores of packed spice ingredients, technicians performing maintenance tasks of equipment in the production area, as well as the cleaner in the wash bay area. Low exposure to spice dust was assigned to administration staff, national distribution department (receiving and despatch) and the laboratory staff. From each stratum a random sample of workers was selected for environmental monitoring. The random selection was based on the NIOSH OESSM sampling method and on using sample size calculations of the top 10%, with 0.95 confidence level (NIOSH Manual). From each of the selected work areas, a random sample of workers was chosen, ensuring that all job titles were sampled over time (Appendix E). A certified occupational hygienist collected the 62 personal environmental samples during usual production activities under usual circumstances. Field blanks with a minimum of 2 blanks per day and a maximum of 10 blanks for the entire fieldwork period were also collected for analysis.

2.2.3 Aerosol sampling instrumentation and procedure

A personal air-sampling (PAS-6) head attached to a Gillian Gil-3 or -5 pump unit was used to collect the inhalable fraction of spice dust (Lippmann, 1989). Full shift time weighted average samples were obtained from participants. The sampling was done in

accordance with the National Institute for Occupational Safety and Health (NIOSH) method No: 0500 (method for nuisance dust, total), issued 1994 and was compliant with BS EN 1232 for the sampling pumps. The preparation of the PAS-6 sampling heads for the measurement of inhalable dust and the laboratory analysis for total dust particulate concentration, garlic allergen and endotoxin concentrations were done at the National Institute for Occupational Health (NIOH) of National Health Laboratory Service.

Briefly, a pre-weighed filter was inserted in a sterilised filter holder under aseptic conditions, and then sealed with tinfoil. Binder free glass fiber filters i.e. Whatman GF/A filters (millipore; pore size $1.0\mu\text{m}$, 25 mm diameter) were used as the filter medium. The sterile sampling head unit was then packaged and sent to the sampling site. A sampling train was set up with the filter holder fixed near the breathing zone of the participant, generally accepted to extend no more than 30cm from the mouth (therefore on the upper chest, close to the collar-bone), with the inlet pointed downwards. Sampling pumps were calibrated before and after sampling using a bubble flow meter to verify that the air sampling rate had been constant. An automatic flow control was in place that kept the volumetric flow rate constant within ± 0.1 litre/min in the case of changing returned/back-pressure. If the two measured flow rates differed by more 0.1 litre/min or 5% (whichever is larger), the sample was considered invalid. Field blanks (about 10%) were collected with a minimum of at least 2 blanks a day and a minimum of 10 blanks for the whole fieldwork period to determine the limit of detection. After sampling, the filters were sealed and transported to the National Institute for Occupational Health (NIOH) laboratory for post sampling weighing, extraction and subsequent analyses. For allergen

determination the extract was reconstituted in 0.15 M phosphate buffered saline (Heederik et al., 1999).

2.2.4 Analysis of samples

2.2.4.1 Analysis of samples for particulate mass

The concentration of dust collected on the sampling filters was measured gravimetrically in accordance with European Standard EN 481, Brussels 1993. Laboratory analysis and the weighing of the filters were done as outlined in MDHS 14/3 2000 (MDHS 14/3 2000).

The airborne dust concentration was calculated using the sampling time, the mean flow and the dust yield. This is the difference of filter weight after and before sampling corrected for the arithmetic means of the blanks. The average weight change of the blank substrates was subtracted from the weight change of each sample substrate, in order to calculate the net weight gain. The mean flow is the arithmetic mean of the flow at the start of the sampling (2.0 ± 0.1 litre/min) and the flow after sampling. The difference in flow should not exceed 10% of the initial flow.

The calculation of dust concentration is summarised as follows: the volume of air passing through the sampler was calculated by multiplying the mean volumetric flow rate in cubic metres per minute by the sampling time in minutes (flow rate in litre/min = 1000 x flow rate in m^3/min). The net weight gain (mg) of the sample

substrate was divided by the volume air sampled (m^3) to give the average dust concentration in milligrams per cubic metre of air (mg/m^3).

2.2.4.2 Analysis of samples for garlic allergen concentration

Methods specifically for the detection of garlic allergens were developed with the assistance of Dr A Lopata, RMIT University, Australia, and Dr T Singh, National Institute for Occupational Health (NIOH) of National Health Laboratory Service. Protein extract of garlic was produced and proteins separated by sodium dodecyl sulphate polyacrylamide (SDS) gradient gel-electrophoresis. Thereafter proteins were transferred to a membrane and the presence of allergenic proteins was confirmed by immunoblotting (Western-blot) using serum of sensitised workers known to have garlic allergy. This garlic extract (now called 'garlic-standard') was the reference material for the following inhibition assays and was used to produce a standard curve.

The inhibition procedure was carried out as an additional step before applying the standard assay run as explained under 2.3.2.1. Collected dust on filter membranes was extracted into 0.5 ml phosphate-buffered saline (containing 0.05% Tween-20) overnight on a shaker at 4 °C. The supernatants were removed and stored at -20 °C until further use (Lopata et al., 2005). These extracts (now termed 'dust-extract') were used for the inhibition assay to quantify the amount of allergenic garlic proteins. Dilutions of this dust-extract, as well as garlic-standard (four different concentrations were sufficient), were produced in 'dilution buffer' (0.1 M phosphate buffer, pH 7.4) and pre-incubated with serum (ratio 50 μl extract plus 50 μl serum) for 3 hours at 4 °C in a reagent tube. Subsequently this serum-allergen mixture was added to the garlic

ImmunoCAP (Phadia AB, Uppsala, Sweden) and the amount of residual specific IgE antibody quantified using the standard procedure as indicated in section 2.3.2.1. The amount of garlic allergen in the dust-sample was calculated from the standard-curve produced with garlic-extract.

2.2.4.3 Analysis of samples for endotoxin concentration

The NIOH laboratory determined the concentration of bacterial endotoxin in the airborne particulate dust, using methodology previously described (Spaan et al., 2007). Samples were extracted in endotoxin free water plus 0.05% Tween 20. The sample was shaken on a horizontal shaker for 1 hour at room temperature. Aliquots were stored at -70°C until analysis.

The chromogenic-1000 limulus amoebocyte lysate (LAL) assay (Cambrex Bio Science Walkersville, USA) was used. Throughout the analytical process, endotoxin free products, including water was used. Endotoxin analysis was done according to the manufacturer's instructions. Water negative controls were included with each analysis. Standards were made using the standard *Escherichia coli* provided in the kit. The curve included 0.1, 0.25, 0.5 and 1 EU/ml (including 0.4 EU/ml for positive control). All standards and samples were vortexed for 90 seconds before use. Briefly, a 50µl of blank, standard and sample was pipetted in duplicate into a pre-warmed (37°C) sterile 96-well microtitre plate (Nunc, Denmark). Using a multi channel pipette, 50µl of reconstituted Lysate was pipetted into each well and incubated for 10 minutes. After incubation 100µl of reconstituted substrate was added to each well and incubated for 6 minutes. After 6 minutes, 50µl of a 25% acetic acid solution was

added to each well to stop the reaction. The plates were read at 405nm. Change in absorbance relative to the assay reagent blank was calculated, and a standard curve of delta absorbance versus endotoxin activity was generated. Assays in which the standard curve had a correlation coefficient ≥ 0.98 and samples with a coefficient of variation $\leq 10\%$ were accepted. Using the calculated volume of air sampled, the results were expressed as EU/m³. The formula: [EU/ml X sample volume (ml)] / [time (min) X (rate (L/min) X 1m³/1000L)] (BioWhittaker, 2001).

2.3 Health outcome assessment

2.3.1 Respiratory questionnaire

Each worker answered a standard questionnaire specifically designed for the investigation of asthma contained in the Protocol for the European Community Respiratory Health Survey (Burney et al., 1994). It addressed acute and chronic work-related respiratory and dermatological symptoms and a history of previous medical illnesses. In addition, it included questions relating to current and previous employment, degrees of exposure to spice dust and tobacco smoke. The questionnaire had been modified for local conditions in a spice mill and was used in English only with validity and reproducibility confirmed in previous studies (Burney et al., 1994). Trained interviewers in English in which the workers were fluent administered the questionnaire. Smoking status was classified into three categories viz. non-smoker as lifelong abstinence from smoking; ex-smoker if ceased smoking completely more than one month before the survey; and current smoker. Environmental exposure in the questionnaire was assessed by: workers' description of job in a specific work area;

distance from dust/aerosol source; subjective categorisation of exposure to aerosols into low, medium or high categories according to work process areas; use of personal protective equipment e.g. respirators, goggles, gloves (this was validated by or combined with written job histories). Past medical history (atopy) prior to and after employment in the spice industry was assessed by presence of any one of the following: chronic runny nose/itchy eyes, skin rashes/eczema, history of hay fever, or asthma in childhood. Acute and chronic symptom variables evaluated for temporal relation to work included: respiratory (wheeze, tight chest, cough and shortness of breath); skin (itchy skin, skin rash, wheals); ocular (itchy eyes, red nasal runny nose, blocked nose, stuffy nose) symptoms. Questions were also asked regarding dietary factors and domestic activities, which included consumption of a selection of 20 different types of spices, products containing wheat such as bread and spicy food preparation activities at home (Appendix F).

2.3.2 Immunological assessment

2.3.2.1 Phadiotop and allergen-specific serum IgE

A qualified nursing sister took a blood sample (9 ml) from each worker using a Becton Dickinson Vacutainer SST tube (with gel medium and clot activator). The blood was allowed to clot for 1-2 hours at room temperature (20-24 degrees Celsius). The sample was then centrifuged at 1350g for 10 minutes at room temperature at the Allergy Diagnostic and Clinical Research Unit (ADCRU), University of Cape Town. The serum was then transferred to another tube and stored at -20 degrees Celsius until assayed for further measurement. The quantification of specific IgE to specific

occupational allergens (garlic, chili pepper, wheat) was performed using the UniCAP system (ImmunoCAP: Phadia AB, Uppsala, Sweden). A trained technologist, blinded with regard to the exposure history, performed the analysis. While conducting the analysis for one allergy marker, the technologist was also blinded with regard to the results of the other markers in that batch. Aliquots of serum obtained for doing the ImmunoCAP analysis were frozen at -80 degrees Celsius and stored in the expectation that funding may become available in the near future for characterizing the molecular structure of specific antigens responsible for allergic sensitisation to spices.

The standard UniCAP assay procedure was used for the analysis of the samples by the National Health Laboratory Service, NIOH. The more sensitive standard curve for specific IgE, which has a limit of detection (LoD) of 0.1 kU_A/l, was used, as very low levels of specific IgE may still demonstrate an increased probability of allergic reaction (Lopata, 2006). Sensitisation to common aeroallergens was evaluated using ImmunoCAP Phadiotop test. Atopy was defined as a Phadiotop test >0.35kU/l. The definition of sensitisation to specific occupational allergen (garlic, chili pepper, wheat) was defined as a specific IgE concentration >0.35kU/l.

2.3.3 Lung function spirometry

Lung function was measured by spirometry according to guidelines of the American Thoracic Society/European Respiratory Society as set out in ATS/ERS update 2005 (Pellegrino et al., 2005). A flow-volume Koko spirometer was used. The spirometer was calibrated at least twice a day with a three-litre syringe. Three volume calibrations were performed each time. All three of these measured the calibrated

volume to within the 3.5% required accuracy. The temperature and humidity were monitored on a daily basis. An experienced technologist from the UCT Lung Institute conducted spirometry/lung function testing. The technologist was blinded to the exposure status of each worker. Spirometry was performed in a sitting position with nose clips. Each worker performed up to eight trials to produce three acceptable curves. Test reproducibility was used as a guide to whether further attempts will be necessary. Reproducibility criteria were the two best tracings for both FEV₁ and FVC varying by no more than 150 ml or 5%, whichever was greater. However, failure to meet reproducibility criteria did not result in exclusion of the spirogram results from the statistical analysis. Poor reproducibility may also be an independent marker of airway dysfunction (Becklake and White, 1993). The lung function indices of primary interest included forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁). The best FEV₁ and FVC were used regardless of whether they belong to the same tracing. Lung volumes obtained by spirometry were adjusted for body temperature and pressure according to the temperature and atmospheric pressure measured on a continuous basis throughout the day. Heights of workers were recorded for calculating predicted lung function indices. Reference values of the European Community for Coal and Steel (ECCS) were used for spirometry interpretation, with lower limits corresponding to the 95th percentile (Quanjer et al., 1993). Spirometry assessment was done during the working day in the latter part of the week (towards the end of the shift). The spirometry was done before and after inhalation of a bronchodilator, short-acting β^2 -agonist salbutamol, and four separate doses of 100 μ g using a metered dose inhaler without a spacer. Significant airway reversibility was defined as an increase in FEV₁ \geq 12% and \geq 200ml absolute increase 15 minutes post-bronchodilator administration. To standardise results, pre- and post-bronchodilator

lung function testing was done on each worker, ensuring detection of small airway and early airflow obstruction. Special instructions were given to workers to ensure that tested individuals did not smoke tobacco (at least 2 hours before) and did not use any anti-asthmatic inhalers (12 hours before) or oral asthma medications (48 hours before) prior to the test (Appendix G, H).

2.3.4 Fractional exhaled nitric oxide (FE_{NO})

A hand-held portable nitric oxide sampling device (NIOX MINO[®] Airway Inflammation Monitor; Aerocrine AB, Solna, Sweden) was used to measure FE_{NO} via an electrochemical sensor (Menzies et al., 2007). The worker was seated comfortably, with the mouthpiece at the proper height and position. A nose clip was not used, as this may allow nasal nitric oxide (NO) to accumulate and promote leakage of this nitric oxide via the posterior nasopharynx. The worker inserted a mouthpiece and inhaled deeply over 2 to 2.5 seconds through the mouth to total lung capacity (TLC) and then exhaled immediately, slow and with a constant flow rate for 5-30 seconds, as breath holding might affect FE_{NO} levels. Three technically adequate measurements were performed in line with the current American Thoracic Society /European Respiratory Society recommendations (ATS/ERS 2005 Recommendations). Fractional concentration of exhaled nitric oxide (FE_{NO}) measurements were done before and after the work shift and prior to the following shift. Each worker was not exposed to spice dust for 48 hours prior to testing. The timing of an FE_{NO} measurement after exposure to a specific agent may also affect the level of exhaled nitric oxide collected (Kharitonov et al., 1997). Special instructions were provided to workers to ensure that tested individuals did not smoke tobacco, eat or drink (at least

1 hour before) prior to the test. A pre-test questionnaire was administered prior to testing to collect information on recent chest infections, smoking, alcohol consumption, green vegetable consumption, medication usage, recent exercise and previous lung function testing. No FE_{NO} measurements were performed at the time of an upper respiratory tract infection or up to 4 weeks following (Kharitonov et al., 1997). A blood pressure reading was documented for each worker. Ambient nitric oxide measurements and temperature were also recorded (Appendix I, J). Absolute FE_{NO} values are expressed in ppb, and changes across shift and across 24 hours are expressed as a percentage of the initial value ($\Delta\%$).

Since fractional exhaled nitric oxide (FE_{NO}) is a relatively new instrument, various approaches have been used to detect evidence of airway inflammation related to asthma. Some studies have shown that in inhaled corticosteroids (ICS) naïve patients, $FE_{NO} > 35$ ppb predicted asthma control improvement in response to inhaled corticosteroids with a positive predictive value (PPV) of 68% (Michilis et al., 2008). Other studies showed that following steroid withdrawal, an absolute value for FE_{NO} of 15ppb or greater, or an increase of more than 10ppb or 60% over baseline, is a useful threshold for the detection of ongoing airway inflammation, as well as predicting the advent of breakthrough symptoms (Jones et al., 2001). More recent results from a study of asthma in general practice showed that asthma could be ruled in with levels of $FE_{NO} > 46$ ppb and mild to moderate asthma could be ruled out with levels of $FE_{NO} \leq 12$ ppb measurements (Schneider et al., 2009).

In this cross-sectional study FE_{NO} cut-off >15ppb (median of the baseline pre-shift FE_{NO} levels of this population) and >50ppb (probable asthma) were used during analysis of baseline FE_{NO} levels to identify abnormal results.

2.4 Data management and analysis

2.4.1 Data management

The Information Technology Services at the University of Cape Town captured all the data from questionnaires using double data entry procedures. All questionnaires were stored in confidential files until the completion of the study. Each individual who agreed to participate was assigned a unique 3-digit code. All data collection instruments, as well as all biological specimen containers, reflected this 3-digit code. The entire database, questionnaires and laboratory test results, were analyzed using STATA version no 8. Independent checks of range, validity, consistency and missing data were performed. Logic check programs were run to ensure that each value found in the data fell within the expected range or corresponded to possible values in the codebook and the study coordinator resolved discrepancies. STATA 8 statistical package was utilized for data management using Stata 8 computer software (StataCorp).

2.4.2 Data analysis

Key associations of interest involved investigating relationships between risk factor variables (exposure status, host factor attributes) and health outcomes (respiratory

symptoms, immunological status, pulmonary function, fractional exhaled nitric oxide).

2.4.2.1 Outcome variables

The key outcome variables of interest included:

- WRURS = work-related upper respiratory symptoms defined as the presence of symptoms of work-related nasal and ocular irritation i.e. sneezy/itchy/runny nose or red/itchy/watery eyes.
- WRURS due to spice = work-related upper respiratory symptoms due to spice dust defined as the presence of sneezy/ itchy/runny nose and or red/itchy/watery eyes related to spices at work.
- WRLRS = work-related lower respiratory symptoms defined as the presence of symptoms of work-related chest tightness or wheeze.
- WRLRS due to spice = work-related lower respiratory symptoms due to spice dust defined as the presence of symptoms of chest tightness and wheeze caused by spice as reported by the worker.
- allergic sensitisation (as measured by antigen-specific circulating IgE antibodies in human serum to specified occupational allergens garlic, chili pepper, wheat)
- airway inflammation (as measured by elevated fractional concentration of exhaled nitric oxide) suggestive of asthma (FE_{NO} levels >50ppb)

- occupational rhinitis/conjunctivitis (work-related specific symptom/s and presence of allergic sensitisation to occupational allergens garlic, chili pepper, wheat)
- occupational asthma due to one or more spice allergens (defined by presence of both allergic sensitisation to specified spice allergens and the presence of reversible airflow obstruction on spirometry with the presence of self-reported work-related symptoms chest tightness and/or wheeze)

2.4.2.2 Exposure variables

The primary measures of exposure included:

- exposure to inhalable spice dust particulate mass concentration in current job
- exposure to inhalable garlic allergen concentration in current job
- exposure to inhalable endotoxin concentration in current job

2.4.2.3 Covariates

- age
- sex/gender
- smoking status (current, ex-smoker, never smoker)
- atopy (Phadiotop test >0.35kU/l)

2.4.3 Statistical analysis

Analyses were conducted using STATA 8 statistical package. Univariate, bivariate and multivariate analyses were performed for relevant outcome variables. Univariate analyses summarised the distribution of each measured variable. Exploratory bivariate analyses were used to assess the nature of the associations between outcomes, exposure and covariates. Both continuous and categorical analyses were considered. Skewed variables such as exposure metrics and IgE levels were log transformed before model development. Multivariate logistic regression models were developed to assess the exposure effects on the health outcomes. Generalised linear and/or additive models were used for multivariate analyses with individual continuous and dichotomous outcomes and categorical and/or continuous exposures and covariates. Confounding and effect modification by covariates were considered in the formulation of the models. The confounders/covariates included in multivariate analysis model were based on ($p < 0.05$) level of significance of association with outcome measures.

2.5 Human subject and ethical issues

2.5.1 Ethics

The Human Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town approved the epidemiological study “Determinants of

Occupational Allergy to Spices among Spice Mill Workers”. The ethics approval number is 179/2008 (Appendix B).

Consent forms, briefing documents, medical report forms, and guideline for assessing and managing medical screening results are set out in the following appendices (C, D, K, L).

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Chapter 3

Results

A total of 150 spice mill workers were evaluated in this study. The overall response rate was 94% for most aspects of the health assessment except for lung function spirometry with a slightly reduced response rate (93%) due to workers having left the industry before the study was completed.

3.1 Environmental exposure assessment

A total of 62 samples was collected during personal environmental sampling. In the spice mill the blending/sifting work area demonstrated the highest exposure levels for inhalable dust particulate (GM 5.78 mg/m³; range 0.23-47.64 mg/m³) (Table 3.1.1) as well as for inhalable garlic allergen (GM 3.71 µg/m³; range 0.05-43.29 µg/m³) (Table 3.1.2) while the milling section showing the highest exposure levels for endotoxin concentration (GM 124.22 EU/m³; range 43.87-389.74 EU/m³) (Table 3.1.3). Garlic allergen levels were up to ten times more in the blending/sifting area versus other work areas. All together blending/sifting, packing and milling work areas measured higher levels for inhalable dust particulate (GM >3.78 mg/m³), garlic allergen (GM >0.235 µg/m³) and endotoxin concentration (GM >59.06 EU/m³). The weighing area had high inhalable dust particulate (GM 4.32 mg/m³; range 2.49-9.19) and garlic allergen (GM 0.76 µg/m³; range 0.13-6.01) exposure levels, but low endotoxin concentration levels (GM <44.86 EU/m³). Administration department had low levels for all three categories of exposure. A strongly positive correlation was demonstrated

between particulate dust and garlic allergen levels ($r=0.70$; $p<0.001$) and a modest degree of positive correlation between particulate dust and endotoxin levels ($r=0.43$; $p<0.001$) as well as for garlic allergen and endotoxin levels ($r=0.37$; $p<0.05$) (Table 3.1.1-3.1.4; Figure 3.1- 3.3).

Table 3.1.1 Personal ambient inhalable dust particulate exposure levels of spice mill workers

Department	Particulate mass concentration (mg/m ³)				
	n	AM	GM	GSD	Range
Blending/sifting	10	11.81	5.78	4.47	0.23-47.64
Weighing	4	4.87	4.32	1.72	2.49-9.19
Packing	17	4.53	3.48	2.05	1.37-15.24
Milling	5	3.91	3.87	1.18	3.22-4.59
Maintenance (production)	4	1.33	1.03	2.49	0.31-2.36
Stores	6	1.20	1.06	1.75	0.49-2.22
Receiving/dispatch	7	0.84	0.74	1.70	0.33-1.57
Food laboratory	6	0.57	0.60	1.91	LOD-1.16
Administration	3	0.54	0.37	2.82	0.17-1.19
Overall	62	4.15	2.06	3.33	LOD-47.64

Note: n number of workers; AM arithmetic mean; GM geometric mean; GSD geometric standard deviation; LOD limit of detection.

Table 3.1.2 Personal ambient inhalable garlic allergen exposure levels of spice mill workers

Department	Garlic allergen concentration (µg/m ³)				
	n	AM	GM	GSD	Range
Blending/sifting	10	10.68	3.71	7.91	0.05-43.29
Packing	16	3.79	0.32	7.99	0.04-40.02
Weighing	4	2.13	0.76	6.47	0.13-6.01
Maintenance (production)	4	0.63	0.18	6.41	0.03-2.20
Milling	5	0.28	0.19	2.86	0.04-0.65
Food laboratory	6	0.09	0.07	2.10	0.03-0.22
Receiving/despatch	7	0.05	0.05	1.60	0.03-0.09
Stores	6	0.05	0.04	1.50	0.03-0.07
Administration	3	0.03	0.03	1.48	0.02-0.05
Overall	61	2.97	0.24	8.42	0.02-43.29

Note: n number of workers; AM arithmetic mean; GM geometric mean; GSD geometric standard deviation.

Table 3.1.3 Personal ambient inhalable endotoxin exposure levels of spice mill workers

Department	Endotoxin concentration (EU/m ³)				
	n	AM	GM	GSD	Range
Milling	5	161.08	124.22	2.24	43.87-389.74
Blending/sifting	10	100.73	74.80	2.02	43.15-384.83
Packing	17	82.17	70.80	1.72	43.14-204.09
Stores	6	55.17	54.50	1.19	44.47-69.13
Maintenance (production)	4	49.85	46.90	1.47	32.68-81.38
Receiving/dispatch	7	46.34	46.01	1.14	35.02-51.94
Food laboratory	6	43.38	43.26	1.09	36.92-46.77
Administration	3	42.54	42.12	1.19	35.85-50.44
Weighing	4	42.09	39.47	1.53	22.89-57.92
Overall	62	74.53	60.52	1.75	22.89-389.74

Note: n number of workers; AM arithmetic mean; GM geometric mean; GSD geometric standard deviation.

Table 3.1.4 Correlation matrix for various exposure metrics (log-transformed, ln) among spice mill workers

Exposure metric	Inhalable particulate mass (ln)	Endotoxin concentration (ln)
	Pearson's Coefficient (r)	Pearson's Coefficient (r)
Endotoxin concentration (ln)	0.43**	-
Garlic allergen concentration (ln)	0.70**	0.37*

Note: *p<0.05; **p<0.001

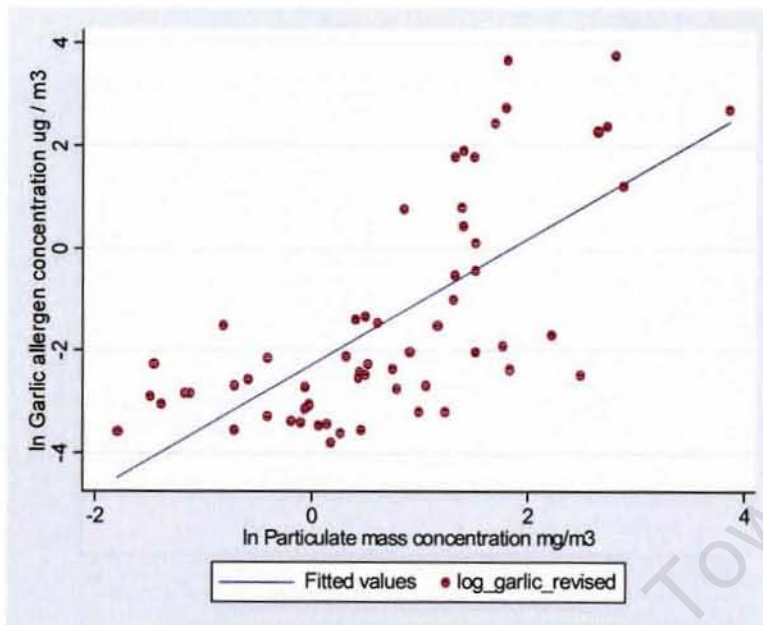


Figure 3.1 Correlation between particulate mass concentration (ln particulate mass mg/m³) and garlic allergen concentration (ln garlic allergen µg/m³) among spice mill workers (n=62)

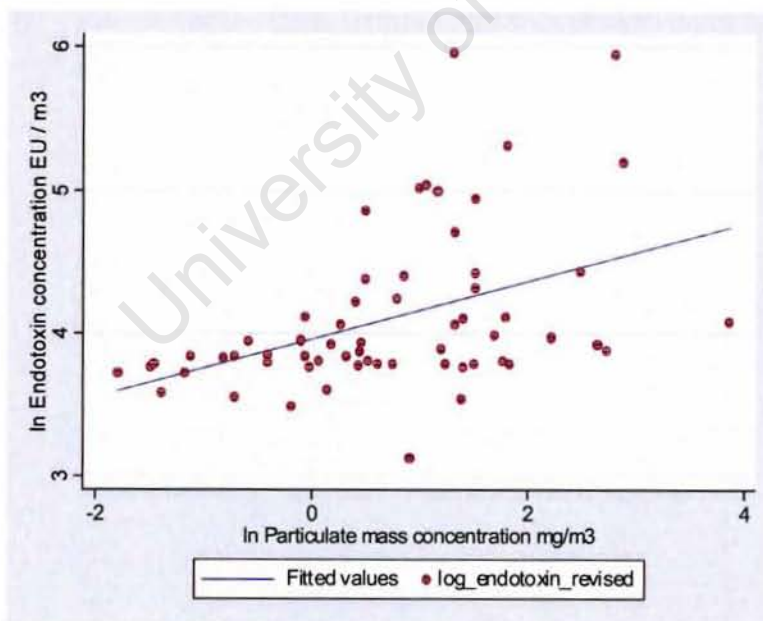


Figure 3.2 Correlation between particulate mass concentration (ln particulate mass mg/m³) and endotoxin concentration (ln endotoxin EU/m³) among spice mill workers (n=62)

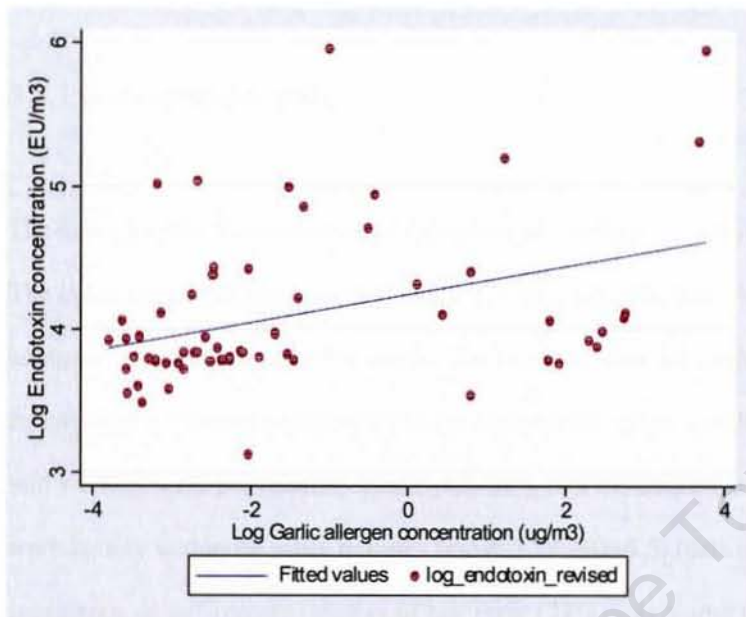


Figure 3.3 Correlation between garlic allergen concentration (ln garlic allergen $\mu\text{g}/\text{m}^3$) and endotoxin concentration (ln endotoxin EU/m^3) among spice mill workers (n=62)

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3.2 Health outcome assessment

3.2.1 Demographic data

The demographic characteristics of the spice mill workers are outlined in Table 3.2.1. The mean age of this predominantly male (71%) workforce was 33.4 years with 46% being current smokers and 45% atopic. The mean duration of employment in the factory was 6.9 years and 3.2 years in the current job. At the time 93% of the spice mill workers were permanently employed. Only two workers presented with a prior work history within the spice industry (mean 3.79; SD±4.5) (data not shown). The prevalence of self-reported history of hay fever (24%) was higher than asthma (9%). A relatively high proportion (10%) of workers reported adverse reactions to spice/food/fruit products. There were 35% with a history of atopy-related symptoms in this group.

Table 3.2.1 Demographic characteristics of spice mill workers

Demographic characteristics	(n=150)
Age (years)	33.4 ± 7.7
Gender (%M:F)	71:29
Smoking status	
current smokers	69 (46%)
ex-smokers	15 (10%)
non-smokers	66 (44%)
Height (metres)	
female	1.59 ± 0.07
male	1.72 ± 0.07
Employment history	
employment duration in current spice mill (years)	6.93 ± 5.6
employment duration in current job (years)	3.23 ± 3.4
Current employment status	
permanent	139 (93%)
casual	11 (7%)
Past history of allergy (self-reported)	
hay fever	36 (24%)
asthma	14 (9%)
eczema	4 (3%)
allergy symptoms related to common inhalants	52 (35%)
family history of atopy	30 (20%)
self-reported adverse reactions to spice/food/fruit products	15 (10%)
other self-reported allergy (insect sting/bites and/or medicine)	10 (7%)
Past history of lung disease (self-reported)	
repeated childhood chest infection	3 (2%)
previous treatment for tuberculosis	6 (4%)
previous treatment for chronic bronchitis	6 (4%)

Note: Continuous variables, mean ± SD; Categorical variables, number (%)

3.2.2 Prevalence of respiratory symptoms

The prevalence of upper respiratory symptoms in the last year ranged from 11%-17% with a history of hay fever in 24% of subjects (Table 3.2.2). The prevalence of lower respiratory symptoms in the past year ranged from 3%-27%. Symptoms suggestive of asthma such as being woken up by a tight chest (10%) and wheezing /whistling in the chest (11%) was similar to the prevalence of doctor-diagnosed asthma (9%). There was 5% of workers with chest symptoms that were caused/worsened by spices/spicy foods.

A high work-related component was demonstrated for respiratory symptoms within this study population due to a prevalence of 43% for work-related (WR) ocular-nasal symptoms, 17% for work-related asthma symptoms due to spice dust and 7% having changed jobs due to work-related chest symptoms.

Table 3.2.2 Prevalence of respiratory symptoms among spice mill workers (n=150)

Respiratory symptom history	
Upper respiratory symptoms	
Ocular-nasal symptoms such as hay fever in the past	36 (24%)
Ocular-nasal symptoms in the last year without having a cold	25 (17%)
Ocular-nasal symptoms triggered by seasonal change	17 (11%)
Current use of hay fever medication	13 (9%)
Work-related upper respiratory symptoms	
Work-related ocular-nasal symptoms	71 (47%)
Work-related ocular-nasal symptoms caused by inhaling spice dust	64 (43%)
Lower respiratory symptoms	
Chest symptoms	
Wheezing or whistling in chest in the past year	17 (11%)
Wheezing or whistling symptoms without having a cold	4 (3%)
Woken up by tight chest in the past year	15 (10%)
Shortness of breath in the past year	8 (5%)
Attack of shortness of breath following exercise in the past year	30 (20%)
Woken up by shortness of breath in the past year	8 (5%)
Woken up by cough in the past year	40 (27%)
Cough most days/nights for 3 or more months in each of last 2 years	6 (4%)
Bring up phlegm on most days/nights for 3 or more months in each of last 2 years	2 (1%)
Shortness of breath when hurrying on level ground or walking up a slight hill	39 (26%)
Asthma history	
Doctor diagnosed asthma	13 (9%)
- <17 years	8 (5%)
- >17 years	6 (4%)
Asthma attack in the last year	3 (2%)
During different seasons of year	8 (5%)
Caused/worsened by weather change	7 (5%)
Caused/worsened by contact with animals/pets	1 (1%)
Caused/worsened by exposure to grass/flowers	3 (2%)
Caused/worsened by heavy exercise	5 (3%)
Asthma symptoms caused/worsened by breathing cold air	2 (1%)
Chest symptoms caused/worsened by spices/spicy foods	7 (5%)
Current use of asthma medication	10 (7%)
Work-related asthma symptom experience	
Work-related asthma symptoms (tight chest or wheezing)	26 (17%)
Work-related asthma symptoms caused by inhaling spice dust	25 (17%)
Ever inhaled an excessive amount of dust/vapours/mist	25 (17%)
Job change due to work-related chest symptoms	10 (7%)

Note: Continuous variables, mean \pm SD; Categorical variables, number (%).

3.2.3 Specific IgE sensitisation profiles to spice dust allergens

In this group of spice mill workers the prevalence for atopy on Phadiotop test was 45%. The specific IgE profiles for spice dust allergens among the workers showed that the prevalence for allergic sensitisation to occupational allergen garlic (19%) was higher than for wheat (9%) and chili pepper (6%). Sensitisation was significantly associated with atopic status (Table 3.2.3a). There was no significant association between sensitisation to occupational allergens (garlic, chili pepper, wheat) and the smoking status of the spice mill workers (data not shown). A very high degree of positive correlation was demonstrated between sensitisation to all three occupational allergens' (garlic, chili pepper, wheat) on specific IgE profiles ($r=0.89-0.96$) (Table 3.2.3b).

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Table 3.2.3a Specific IgE profiles for sensitisation to spice dust allergens among spice mill workers stratified by atopic status

Occupational allergen sensitisation	Overall (n=150)	Atopic (n=67)	Non-atopic (n=83)	p-value
Garlic	29 (19%)	22 (33%)	7 (8%)	<0.001
Chili pepper	9 (6%)	9 (13%)	0	0.001 [#]
Wheat	14 (9%)	14 (21%)	0	<0.001
At least one spice dust allergen	31 (21%)	24 (36%)	7 (8%)	<0.001

Note: Serum specific IgE >0.35kU/l; Atopy: Phadiotop >0.35kU/l (45%); [#]Fisher's exact.

Table 3.2.3b Correlation matrix for sensitisation to various spice dust allergens

Allergic sensitisation metric	Wheat specific IgE (ln)	Chili pepper specific IgE (ln)
	Pearson's Coefficient (r)	Pearson's Coefficient (r)
Garlic specific IgE (ln)	0.94**	0.89**
Wheat specific IgE (ln)	-	0.96**

Note: *p<0.05; **p<0.001

3.2.4 Lung function spirometry indices

A high prevalence of spice mill workers (13%) had evidence of airway obstruction ($FEV_1 < 80\%$ predicted) with 6% demonstrating chronic obstructive pulmonary disease (COPD) ($FEV_1/FVC < 70\%$) and 4% showing significant reversibility of airflow obstruction (FEV_1 increase $\geq 12\%$ and ≥ 200 ml post-bronchodilator) (Table 3.2.4).

Table 3.2.4 Lung function indices among spice mill workers stratified by gender

Pulmonary function indices	Overall (n=143)	Males (n=105)	Females (n=38)	p-value
FEV_1 (litres)	3.5 ± 0.73	3.71 ± 0.63	2.80 ± 0.52	<0.001
FVC (litres)	4.32 ± 0.89	4.64 ± 0.71	3.44 ± 0.71	<0.001
PEFR (l/sec)	8.06 ± 1.70	8.64 ± 1.50	6.45 ± 1.11	<0.001
$FEV_1\%$ predicted	95.31 ± 13.73	94.57 ± 12.96	97.34 ± 15.67	0.288
FVC% predicted	100.55 ± 13.78	99.35 ± 11.55	103.87 ± 18.39	0.083
PEFR% predicted	94.06 ± 14.80	93.13 ± 14.55	96.63 ± 15.40	0.213
FEV_1/FVC	0.80 ± 0.06	0.80 ± 0.06	0.82 ± 0.06	0.157
No. with $FEV_1 < 80\%$ predicted	19 (13%)	14 (13%)	5 (13%)	0.978
No. with FVC < 80% predicted	4 (3%)	2 (2%)	2 (5%)	0.287 ^δ
No. with PEFR < 80% predicted	27 (19%)	21 (20%)	6 (16%)	0.570
No. with $FEV_1/FVC < 70\%$	8 (6%)	6 (6%)	2 (5%)	1.000 ^δ
No. with FEV_1 increase $\geq 12\%$ and ≥ 200 ml post-bronchodilator	6 (4%)	6 (4%)	0	0.342 ^δ

Note: Continuous variables, mean ±SD; Categorical variables, number (%); Reference values are from the European Community for Coal and Steel (ECCS) 1993; ^δ Fisher's exact test.

3.2.5 Fractional exhaled nitric oxide (FE_{NO}) indices

3.2.5.1 Fractional exhaled nitric oxide (FE_{NO}) levels at baseline, across shift and across 24-hour period

The baseline fractional exhaled nitric oxide (FE_{NO}) levels among the spice mill workers are summarised in Table 3.2.5.1a. The baseline pre-shift FE_{NO} levels had a geometric mean of 14.90ppb. The mean change across shift (GM 15.43ppb) was very similar to the mean change across 24-hour period (GM 15.84ppb) in fractional exhaled nitric oxide (FE_{NO}) levels.

A slightly lower proportion of spice mill workers showed a $\geq 10\%$ change across shift (23%) from baseline FE_{NO} than over the 24-hour period (27%) (data not shown). A similar trend was also observed for workers with FE_{NO} > 10ppb or an increase of FE_{NO} > 60% over baseline (Table 3.2.5.1b).

Table 3.2.5.1a Fractional exhaled nitric oxide (FE_{NO}) levels in spice mill workers (n=150)

FE _{NO} (ppb)	AM	GM	GSD	Range
D1 pre-shift	20.26	14.90	2.12	4 - 157.3
D1 post-shift	19.75	14.16	2.20	4 - 147.7
D2 pre-shift	20.12	14.32	2.19	4 - 161.3
Across shift change (day 1)	- 1.57	15.43	2.53	- 60 - 209.3
Across 24-hour period change	2.47	15.84	2.97	- 45.8 - 537.5

Note: AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation.

Table 3.2.5.1b Fractional exhaled nitric oxide (FE_{NO}) levels increase across shift and across 24-hour period

FE _{NO} (ppb)	No and %	No and %
Absolute change	Across shift	Across 24-hour period
>10	5 (3%)	11 (7%)
FE _{NO} (ppb)	No and %	No and %
% Change	Across shift	Across 24-hour period
>60% from baseline	4 (3%)	8 (5%)

Note: Categorical variables, number (%)

3.2.5.2 Determinants of baseline pre-shift FE_{NO} (ln) levels

The univariate linear model showed that demographic factors such as atopy ($r^2=0.09$, $p<0.001$) and smoking ($r^2=0.09$, $p<0.001$) explained the most variability observed in the baseline pre-shift FE_{NO} levels (Table 3.2.5.2). Atopy showed a significant increase ($\beta=0.44$) and smoking a significant decrease ($\beta=-0.45$) in baseline FE_{NO} levels. As for occupational allergic sensitisation, garlic ($r^2=0.03$, $p=0.049$) and chili pepper ($r^2=0.06$, $p=0.004$) explained the most significant variability in baseline pre-shift FE_{NO} levels with the latter showing greater variability than garlic allergen.

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Table 3.2.5.2 Demographic factors and univariate analysis of determinants associated with baseline pre-shift FE_{NO} (In) levels among spice mill workers

Determinant (n=150)	Mean ± SD	β	r ²	p-value
Age (years)	33.4±7.7	- 0.005	0.0033	0.486
Height (m)	1.68±0.9	1.130	0.0178	0.103
Weight (kg)	74.33±15.9	0.003	0.0048	0.401
BMI (kg/m ²)	26.28±5.7	- 0.002	0.0001	0.892
Blood pressure				
- Systolic (mmHg)	112.63±12.7	0.002	0.0013	0.665
- Diastolic (mmHg)	67.54±9.8	0.0002	0	0.976
	No (%)	β	r²	p-value
Hypertension**	10 (7%)	0.322	0.0115	0.192
Gender (%M:F)	71:29	0.221	0.0181	0.101
Smoking#	69 (46%)	- 0.453	0.0906	<0.001 ^{δδ}
Atopy	67 (45%)	0.444	0.0866	<0.001 ^{δδ}
Recent alcohol intake*	47 (31%)	- 0.029	0.0003	0.830
Recent exercise*	15 (10%)	- 0.261	0.0109	0.203
Recent vegetable intake*	66 (44%)	0.234	0.0239	0.060
Recent steroid use*	6 (4%)	0.297	0.0060	0.345
Reported chest infection***	5 (3%)	-0.181	0.0019	0.599
Lung function test during previous week	4 (3%)	0.640	0.0189	0.093
Allergic sensitisation (specific IgE>0.35kU/l)				
Garlic	29 (19%)	0.305	0.0258	0.049 ^δ
Chili pepper	9 (6%)	0.747	0.0559	0.004 ^δ
Wheat	14 (9%)	0.372	0.0208	0.078
Any spice	31 (21%)	0.263	0.0202	0.083

Note: ^δ p<0.05; ^{δδ} p<0.001; Continuous variables, mean ± SD; Categorical variables, number (%); *Recent = one day ago; **Systolic≥140 and/or Diastolic≥90; ***Self-reported flu or sinusitis in the last three weeks; #Currently smoking.

3.2.5.3 Correlation between FE_{NO} levels and allergen specific IgE

Figures 3.4-3.6 demonstrate the nature of the relationship between baseline pre-shift fractional exhaled nitric oxide (FE_{NO}) levels and specific IgE sensitisation to occupational allergens garlic, chili pepper and wheat. The correlation between baseline pre-shift FE_{NO} levels and specific IgE sensitisation to occupational allergen chili pepper ($r=0.32$, $p<0.001$) and wheat ($r=0.30$, $p<0.001$) was higher than for garlic ($r=0.20$, $p=0.025$).

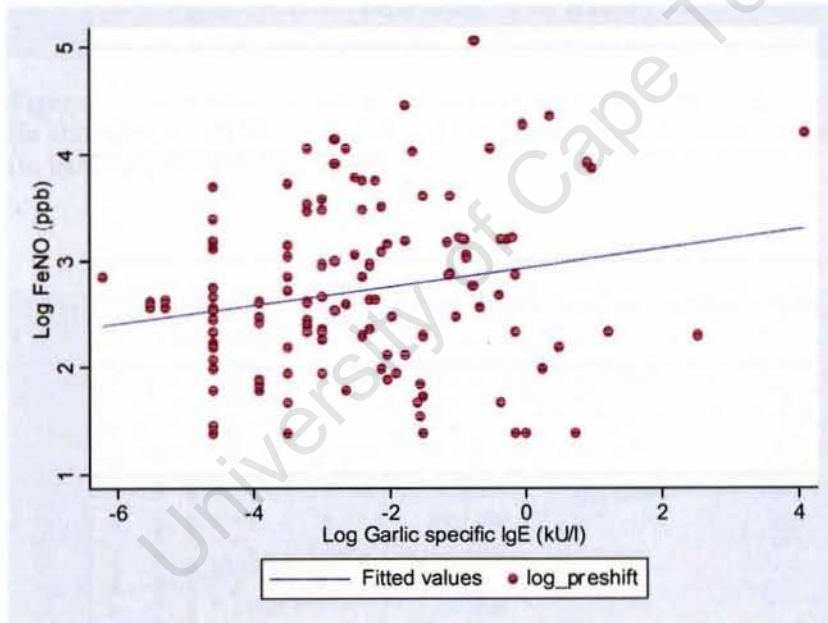


Figure 3.4 Correlation between garlic allergen specific IgE (ln garlic allergen kU/l) and fractional exhaled nitric oxide concentration (ln baseline pre-shift FE_{NO} ppb)

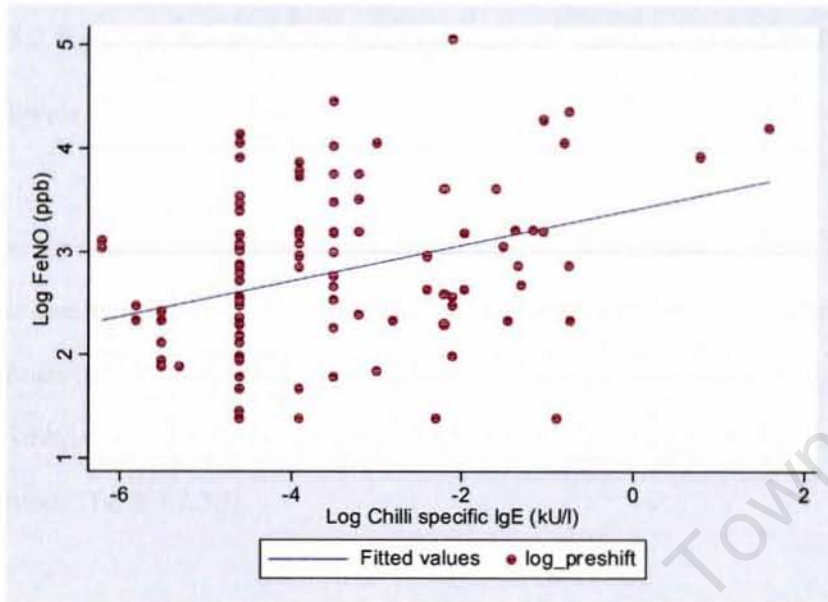


Figure 3.5 Correlation between chili pepper allergen specific IgE (ln chili allergen kU/l) and fractional exhaled nitric oxide concentration (ln baseline pre-shift FE_{NO} ppb)

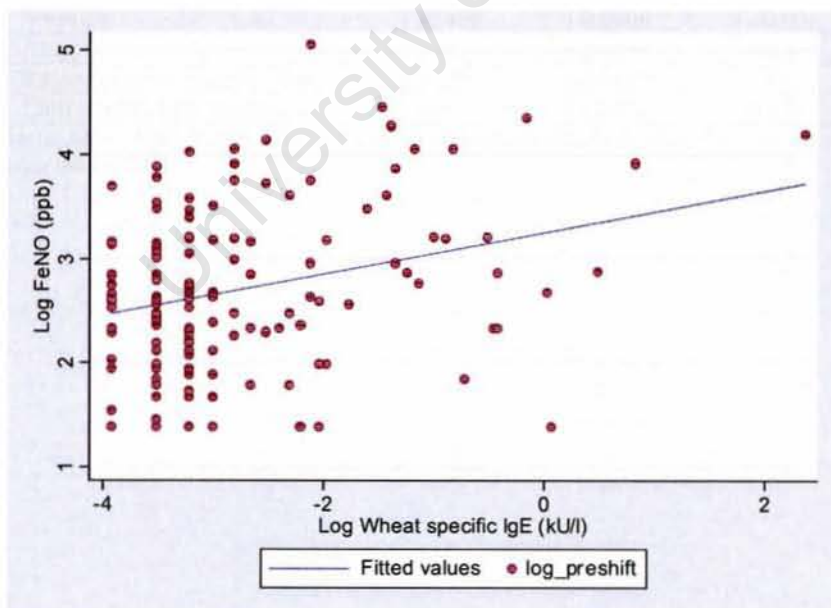


Figure 3.6 Correlation between wheat allergen specific IgE (ln wheat allergen kU/l) and fractional exhaled nitric oxide concentration (ln baseline pre-shift FE_{NO} ppb)

3.2.5.4 Overall model of determinants of baseline pre-shift FE_{NO} (ln) levels

In the final multivariate regression model the main determinants of raised FE_{NO} levels at baseline were atopy ($\beta=0.411$), the intake of green leafy vegetables over the last 24 hours ($\beta=0.279$) and chili pepper IgE-mediated allergic sensitisation ($\beta=0.471$). Smoking ($\beta=-0.468$) showed a significant negative correlation with baseline FE_{NO} levels (Table 3.2.5.4).

Table 3.2.5.4 Multivariate linear regression analysis of factors associated with baseline pre-shift FE_{NO} (ln) levels among spice mill workers

Determinants	β	r^2	p-value
Smoking	-0.468	0.0906	<0.001
Atopy	0.411	0.1830	<0.001
Recent green vegetable intake	0.279	0.2017	0.013
Chili specific IgE sensitisation	0.471	0.2375	0.052

Note: Atopy: Phadiatop>0.35kU/l; Recent green vegetable intake: intake of green leafy vegetables over the last 24hrs.

3.2.5.5 Determinants of FE_{NO} levels at different cut-off points

Table 3.2.5.5 demonstrates the association between host factors and FE_{NO} levels for various cut-off points ppb (9; 13.7; 20; 23.7; 25). A consistently strong association was demonstrated between FE_{NO} levels >13.7ppb and atopy ($\beta=0.35$, $p=0.02$) as well as occupational allergen sensitisation to chili pepper ($\beta=1.31$, $p=0.01$) whereas smoking ($\beta=-0.310$, $p=0.001$) correlated with a decrease in FE_{NO} beyond these levels.

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Table 3.2.5.5 Simultaneous quantile regression (SQR) model showing determinants of the continuous variable FE_{NO} levels

Percentiles FE _{NO}	0.25		0.50		0.67		0.75		0.81	
	9ppb		13.7ppb		20ppb		23.7ppb		25ppb	
Predictor	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
Demographics										
Height (m)	1.716	0.001*	1.217	0.284	1.182	0.209	0.798	0.528	1.274	0.426
Gender (% M:F)	0.343	0.003*	0.206	0.237	0.375	0.142	0.301	0.381	-0.298	0.421
Smoking#	-0.582	<0.001**	-0.310	0.001*	-0.309	0.021*	-0.130	0.555	-0.516	0.041*
Atopy	0.182	0.307	0.351	0.020*	0.813	<0.001**	0.888	<0.001**	0.818	<0.001**
Recent green leafy vegetable intake ^δ	0.482	0.001*	0.288	0.042*	0.223	0.312	0.070	0.760	0.267	0.333
Spirometry in previous week ^{δδ}	0.596	0.521	0.178	0.839	1.243	0.084	1.041	0.135	1.138	0.035*
Work-related symptoms										
Ocular-nasal	-0.389	0.006*	-0.049	0.685	-0.034	0.874	0.041	0.850	0	1.000
Ocular-nasal due to spice	-0.389	0.002*	-0.098	0.459	-0.176	0.374	-0.056	0.789	-0.271	0.292
Chest	-0.310	0.190	0.071	0.818	0.244	0.512	0.351	0.340	0.673	0.063
Chest due to spice	-0.310	0.152	0	1.000	0.315	0.353	0.351	0.297	0.673	0.049*
Specific IgE>0.35kU/l										
Garlic	0.138	0.591	0.438	0.059	0.353	0.208	0.143	0.719	0.733	0.071
Chili pepper	0.674	0.313	1.310	0.013*	1.314	<0.001**	1.099	<0.001**	1.076	<0.001**
Wheat	0.138	0.731	0.275	0.375	0.257	0.581	0.819	0.070	0.861	0.036*

Note: *p<0.05; **p<0.001; ^δRecent = one day ago; ^{δδ}Previous week = one week ago; #Currently smoking.

3.2.6 Prevalence of allergic disease outcomes

In this study, 21% of workers were sensitised to at least one occupational allergen with a large proportion sensitised to garlic (19%). A relatively higher prevalence for work-related ocular-nasal symptoms due to spice dust was shown for workers sensitised to garlic (9%) compared to wheat (5%) and chili pepper (2%) (Table 3.2.6). Spice mill workers sensitised to occupational allergen (garlic, chili pepper, wheat) showed a similar overall prevalence of probable occupational asthma based on reversible FEV₁ (1%) or FE_{NO} >50ppb (3-4%) with latter index demonstrating a higher overall prevalence of probable occupational asthma.

Table 3.2.6 Prevalence of sensitisation and allergic disease outcomes among spice workers sensitised to occupational allergens (n=150)

Allergic disease outcome	Garlic No. (%)	Chili No. (%)	Wheat No. (%)	Any spice No. (%)
Specific IgE sensitisation (kU/l)	29 (19%)	9 (6%)	14 (9%)	31 (21%)
WRURS due to spice	13 (9%)	3 (2%)	8 (5%)	15 (10%)
Probable OA				
- No. with FEV ₁ increase ≥12% and ≥200ml post-bronchodilator	2 (1%)	2 (1%)	2 (1%)	2 (1%)
- FE _{NO} >50 ppb	6 (4%)	5 (3%)	4 (3%)	6 (4%)

Note: Categorical variables, number (%); WRURS: work-related upper respiratory symptoms; OA: occupational asthma; FE_{NO}: fractional exhaled nitric oxide.

3.2.7 Host factors associated with respiratory outcome measures

An unadjusted logistic regression model illustrating the association between host factors atopy, age, gender, smoking and respiratory outcome measures is outlined in Table 3.2.7.

Atopic spice mill workers were more likely to present with elevated FE_{NO} measurements $>15ppb$ (OR 3.23, CI 1.64-6.35, $p=0.001$) and $>50ppb$ (OR 16.11, CI 2.02-128.30, $p=0.009$).

Spice mill workers who were smokers were more likely to present with general work-related upper respiratory symptoms (WRURS) (OR 1.99, CI 1.04-3.82, $p=0.038$), WRURS due to spice dust (OR 2.31, CI 1.19-4.48, $p=0.013$) and general work-related lower respiratory symptoms (OR 2.61, CI 1.08-6.33, $p=0.033$), and less likely to have FE_{NO} measurements $>50ppb$ (OR 0.09, CI 0.01-0.74, $p=0.025$) as well as $>10\%$ across shift increase in FE_{NO} from baseline (OR 0.45, CI 0.20-1.00, $p=0.051$).

There were no associations observed for age and gender in relation to the respiratory outcome measures.

Table 3.2.7 Host factors associated with work-related symptoms, lung function and FE_{NO} levels (n=150)

OUTCOME	No. (%)	No. (%)	Mean ± SD	No. (%)		No. (%)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
	overall	atopy	age	gender (M:F)		smoking	atopy	age	gender (M:F)	smoking
WRURS	71 (47%)	31 (46%)	32.7 ± 7.2	46 (43%)	25 (57%)	39 (56%)	0.93 (0.49-1.76)	0.98 (0.94-1.02)	0.58 (0.29-1.18)	1.99 (1.04-3.82)*
WRURS due to spice	64 (43%)	28 (42%)	32.7 ± 7.1	42 (40%)	22 (50%)	37 (54%)	0.94 (0.49-1.80)	0.98 (0.94-1.02)	0.66 (0.32-1.33)	2.31 (1.19-4.48)*
WRLRS	26 (17%)	14 (21%)	33 ± 6.2	16 (15%)	10 (23%)	17 (25%)	1.56 (0.67-3.65)	0.99 (0.94-1.05)	0.60 (0.25-1.46)	2.61 (1.08-6.33)*
WRLRS due to spice	25 (17%)	14 (21%)	33.2 ± 6.2	15 (14%)	10 (23%)	16 (23%)	1.73 (0.73-4.11)	1.0 (0.94-1.05)	0.56 (0.23-1.37)	2.41 (0.99-5.88)
FEV ₁ /FVC ratio (<0.7)	8 (5.6%)	5 (8%)	38 ± 10.2	6 (6%)	2 (5%)	3 (4%)	2.02 (0.46-8.80)	1.08 (0.99-1.17)	1.09 (0.21-5.65)	0.65 (0.15-2.81)
No. with FEV ₁ increase ≥12% and ≥200ml post-BD	6 (4%)	2 (3%)	31.2 ± 4.7	6 (6%)	0	3 (4%)	0.57 (0.10-3.22)	0.96 (0.85-1.08)	**	1.11 (0.22-5.68)
FE _{NO} >15 ppb	64 (43%)	39 (58%)	32.4 ± 7.9	50 (47%)	14 (32%)	24 (35%)	3.23 (1.64-6.35)*	0.97 (0.93-1.01)	1.91 (0.91-4.01)	0.55 (0.28-1.06)
FE _{NO} >50 ppb	12 (8%)	11 (16%)	34.2 ± 11.1	9 (8%)	3 (7%)	1 (1%)	16.11(2.02-128.30)*	1.02 (0.94-1.09)	1.27 (0.33-4.92)	0.09 (0.01-0.74)*
Across-shift change FE _{NO} >10%	35 (23%)	16 (24%)	34.1 ± 7.9	23 (22%)	12 (27%)	11 (16%)	1.06 (0.49-2.26)	1.02 (0.97-1.07)	0.74 (0.33-1.66)	0.45 (0.20-1.00)
Across 24-hour period change FE _{NO} >10%	40 (27%)	19 (28%)	32.2 ± 7.4	24 (23%)	16 (36%)	16 (23%)	1.17 (0.56-2.41)	0.97 (0.93-1.02)	0.51 (0.24-1.10)	0.72 (0.34-1.49)

Note: *p<0.05; Categorical variables, number (%); Continuous variables, mean ± SD; CI: confidence interval; WRURS: work-related upper respiratory symptoms; WRLRS: work-related lower respiratory symptoms; FE_{NO}: fractional exhaled nitric oxide; OR: each odds ratio is a separate unadjusted regression model for age, gender and smoking status. ** OR calculation not possible due to nil observations for category "reversibility of FEV₁ among females".

The logistic model for FE_{NO} was based on FE_{NO} cut-off points >15ppb (median of the baseline pre-shift FE_{NO} levels) and >50ppb (probable asthma) for analyses.

3.2.8 Environmental factors associated with respiratory outcome measures in unconditional logistic regression models

3.2.8.1 Current airborne particulate mass concentrations as predictor

The association between environmental exposure according to particulate mass and work-related symptoms, occupational allergen sensitisation, lung function and FE_{NO} levels is outlined in Table 3.2.8.1. An unadjusted logistic regression model did not show any significant association between high levels of particulate mass concentration and the presence of work-related upper or lower respiratory symptoms, sensitisation to occupational allergens or lung function measurements.

Table 3.2.8.1 Current airborne particulate mass concentrations as predictor of respiratory outcome measures in spice mill workers

PARTICULATE MASS						
OUTCOME	Overall	Low <1.18 mg/m ³	Medium >1.18 - <3.78 mg/m ³	High >3.78 mg/m ³	Medium vs Low OR	High vs Low OR
Total	n = 150	n = 35	n = 23	n = 92		
	No. (%)	No. (%)	No. (%)	No. (%)	OR (95%CI)	OR (95%CI)
WRURS	71 (47%)	17(49%)	5 (22%)	49 (53%)	0.29 (0.09-0.97)	1.21 (0.55-2.63)
WRURS due to spice	64 (43%)	14(40%)	4 (17%)	46 (50%)	0.32 (0.09-1.13)	1.5 (0.68-3.31)
WRLRS	26 (17%)	3 (9%)	1 (4%)	22 (24%)	0.48 (0.05-5.0)	3.35 (0.94-12.02)
WRLRS due to spice	25 (17%)	3 (9%)	1 (4%)	21 (23%)	0.48 (0.05-5.0)	3.15 (0.88-11.34)
Garlic specific IgE	29 (19%)	5 (14%)	4 (17%)	20 (22%)	1.26 (0.30-5.30)	1.67 (0.57-4.85)
Chili pepper specific IgE	9 (6%)	4 (11%)	2 (9%)	3 (3%)	0.74 (0.12-4.40)	0.26 (0.05-1.23)
Wheat specific IgE	14 (9%)	4 (11%)	2 (9%)	8 (9%)	0.74 (0.12-4.40)	0.74 (0.21-2.63)
At least one spice dust allergen specific IgE	31 (21%)	5 (14%)	4 (17%)	22 (24%)	1.26 (0.30-5.30)	1.89 (0.65-5.45)
FEV ₁ /FVC ratio (<0.7)	8 (6%)	2 (6%)	3 (14%)	3 (3%)	2.45 (0.37-16.01)	0.55 (0.09-3.43)
No. with FEV ₁ increase ≥12% and ≥200ml post-bronchodilator	6 (4%)	0	1 (5%)	5 (6%)	**	**
Baseline FE _{NO} >15ppb	64 (43%)	15 (43%)	14 (61%)	35 (38%)	2.07 (0.71-6.06)	0.82 (0.37-1.80)
Baseline FE _{NO} >50ppb	12 (8%)	5 (14%)	1 (4%)	6 (7%)	0.27 (0.03-2.50)	0.42 (0.12-1.47)
Across-shift change FE _{NO} >10%	35 (23%)	6 (17%)	5 (22%)	24 (26%)	1.34 (0.36-5.05)	1.71 (0.63-4.61)
Across 24-hour period change FE _{NO} >10%	40 (27%)	7 (20%)	8 (35%)	25 (27%)	2.13 (0.65-7.03)	1.49 (0.58-3.85)

Note: Percentages expressed relative to numbers exposed excluding missing data; CI: confidence interval; WRURS: work-related upper respiratory symptoms; WRLRS: work-related lower respiratory symptoms; FE_{NO}: fractional exhaled nitric oxide; OR: Odds ratios derived using symptom odds in low exposure work category as reference category and are unadjusted for age, gender, atopy and smoking status. ** OR calculation not possible due to nil observations for exposure category "Low".

3.2.8.2 Current airborne endotoxin concentrations as predictor

The association between environmental exposure according to endotoxin concentration and work-related symptoms, occupational allergen sensitisation, lung function and FE_{NO} levels is outlined in Table 3.2.8.2. The unadjusted logistic regression models showed a significant increased association between high endotoxin concentration levels (>59.06 EU/m³ versus <44.86 EU/m³) and the development of general work-related lower respiratory symptoms (WRLRS) (OR 6.25, CI 1.38-28.40, p=0.018), as well as WRLRS due to spice dust inhalation (OR 5.83, CI 1.28-26.58, p=0.023).

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Table 3.2.8.2 Current airborne endotoxin concentrations as predictor of respiratory outcome measures in spice mill workers

ENDOTOXIN CONCENTRATION						
OUTCOME	Overall	Low <44.86 EU/ m ³	Medium >44.86 <59.06 EU/ m ³	High >59.06 EU/ m ³	Medium vs Low OR	High vs Low OR
Total	n = 150	n = 37	n = 37	n = 76		
	No. (%)	No. (%)	No. (%)	No. (%)	OR (95%CI)	OR (95%CI)
WRURS	71 (47%)	18 (49%)	11 (30%)	42 (55%)	0.45 (0.17-1.16)	1.30 (0.6-2.87)
WRURS due to spice	64 (43%)	15 (41%)	10 (27%)	39 (51%)	0.54 (0.20-1.44)	1.55 (0.70-3.43)
WRLRS	26 (17%)	2 (5%)	4 (11%)	20 (26%)	2.12 (0.36-12.36)	6.25 (1.38-28.40)*
WRLRS due to spice	25 (17%)	2 (5%)	4 (11%)	19 (25%)	2.12 (0.36-12.36)	5.83 (1.28-26.58)*
Garlic specific IgE	29 (19%)	6 (16%)	8 (22%)	15 (20%)	1.42 (0.44-4.61)	1.27 (0.45-3.60)
Chili pepper specific IgE	9 (6%)	1 (3%)	5 (13%)	3 (4%)	5.62 (0.62-50.72)	1.48 (0.15-14.73)
Wheat specific IgE	14 (9%)	1 (3%)	6 (16%)	7 (9%)	6.97 (0.80-61.07)	3.65 (0.43-30.85)
At least one spice dust allergen specific IgE	31 (21%)	6 (16%)	8 (22%)	17 (22%)	1.42 (0.44-4.61)	1.49 (0.53-4.16)
FEV ₁ /FVC ratio (<0.7)	8 (6%)	1 (3%)	4 (11%)	3 (4%)	4.52 (0.48-42.60)	1.52 (0.15-15.17)
No. with FEV ₁ increase ≥12% and ≥200ml post-bronchodilator	6 (4%)	1 (3%)	1 (3%)	4 (6%)	1.03 (0.06-17.13)	2.06 (0.22-19.13)
Baseline FE _{NO} >15ppb	64 (43%)	14 (38%)	19 (51%)	31 (41%)	1.73 (0.69-4.38)	1.13 (0.50-2.54)
Baseline FE _{NO} >50ppb	12 (8%)	3 (8%)	3 (8%)	6 (8%)	1 (0.19-5.31)	0.97 (0.23-4.12)
Across-shift change FE _{NO} >10%	35 (23%)	9 (24%)	6 (16%)	20 (26%)	0.60 (0.19-1.91)	1.11 (0.45-2.75)
Across 24-hour period change FE _{NO} >10%	40 (27%)	8 (22%)	9 (24%)	23 (30%)	1.16 (0.39-3.45)	1.57 (0.62-3.96)

Note: *p<0.05; Percentages expressed relative to numbers exposed excluding missing data; CI: confidence interval; WRURS: work-related upper respiratory symptoms; WRLRS: work-related lower respiratory symptoms; FE_{NO}: fractional exhaled nitric oxide; OR: Odds ratios derived using symptom odds in low exposure work category as reference category and are unadjusted for age, gender, atopy and smoking status.

3.2.8.3 Current airborne garlic allergen concentrations as predictor

The association between environmental exposure according to garlic allergen concentration and work-related symptoms, occupational allergen sensitisation, lung function and FE_{NO} levels is outlined in Table 3.2.8.3. The unadjusted logistic regression model showed a significant increased association between high levels of inhalable garlic allergen (>0.235µg/m³ versus <0.066µg/m³) and the development of work-related upper respiratory (WRURS) (OR 2.61, CI 1.22-5.58, p=0.01) and work-related lower respiratory (WRLRS) (OR 3.18, CI 1.02-9.89, p=0.046) symptoms due to spice dust, as well as for general WRURS (OR 2.21, CI 1.06-4.58, p=0.03) and WRLRS (OR 3.38, CI 1.09-10.47, p=0.03). Chili pepper sensitisation (OR 0.23, CI 0.05-0.97, p=0.04) showed a significant negative association with high levels of garlic allergen exposure in the unadjusted model. Trend analysis confirmed a significant increase in the prevalence of work-related upper and lower respiratory symptoms across exposure groups, as well as a significant decrease in odds for chili pepper sensitisation across the exposure categories for garlic allergen (p<0.05). A borderline association (p=0.08) was demonstrated for chronic obstructive airway disease defined as FEV₁/FVC ratio (<0.7) with increasing levels of garlic allergen exposure (data not shown).

Table 3.2.8.3 Current airborne garlic allergen concentrations as predictor of respiratory outcome measures in spice mill workers

GARLIC ALLERGEN CONCENTRATION						
OUTCOME	Overall	Low <0.066 µg/m ³	Medium >0.066 <0.235 µg/m ³	High >0.235 µg/m ³	Medium vs Low OR	High vs Low OR
Total	n = 150	n = 47	n = 11	n = 92		
	No. (%)	No. (%)	No. (%)	No. (%)	OR (95%CI)	OR (95%CI)
WRURS	71 (47%)	16 (34%)	6 (54%)	49 (53%)	2.32 (0.61-8.80)	2.21 (1.06-4.58)*
WRURS due to spice	64 (43%)	13 (28%)	5 (45%)	46 (50%)	2.18 (0.57-8.39)	2.61 (1.22-5.58)*
WRLRS	26 (17%)	4 (8%)	0	22 (24%)	**	3.38 (1.09-10.47)*
WRLRS due to spice	25 (17%)	4 (8%)	0	21 (23%)	**	3.18 (1.02-9.89)*
Garlic specific IgE	29 (19%)	9 (19%)	0	20 (22%)	**	1.17 (0.49-2.83)
Chili pepper specific IgE	9 (6%)	6 (13%)	0	3 (3%)	**	0.23 (0.05-0.97)*
Wheat specific IgE	14 (9%)	6 (13%)	0	8 (9%)	**	0.65 (0.21-2.0)
At least one spice dust allergen specific IgE	31 (21%)	9 (19%)	0	22 (24%)	**	1.33 (0.56-3.17)
FEV ₁ /FVC ratio (<0.7)	8 (6%)	5 (11%)	0	3 (3%)	**	0.28 (0.06-1.24)
No. with FEV ₁ increase ≥12% and ≥200ml post-bronchodilator	6 (4%)	1 (2%)	0	5 (6%)	**	2.65 (0.30-23.40)
Baseline FE _{NO} >15ppb	64 (43%)	24 (51%)	5 (45%)	35 (38%)	0.80 (0.21-2.98)	0.59 (0.29-1.20)
Baseline FE _{NO} >50ppb	12 (8%)	5 (11%)	1 (9%)	6 (6%)	0.84 (0.09-8.01)	0.59 (0.17-2.03)
Across-shift change FE _{NO} >10%	35 (23%)	8 (17%)	3 (27%)	24 (26%)	1.83 (0.40-8.44)	1.72 (0.70-4.20)
Across 24-hour period change FE _{NO} >10%	40 (27%)	12 (25%)	3 (27%)	25 (27%)	1.09 (0.25-4.80)	1.09 (0.49-2.42)

Note: *p<0.05; Percentages expressed relative to numbers exposed excluding missing data; CI: confidence interval; WRURS: work-related upper respiratory symptoms; WRLRS: work-related lower respiratory symptoms; FE_{NO}: fractional exhaled nitric oxide; OR: Odds ratios derived using symptom odds in low exposure work category as reference category and are unadjusted for age, gender, atopy and smoking status. ** OR calculation not possible due to nil observations for exposure category "Medium".

3.2.9 Multivariate conditional logistic regression model of environmental factors associated with respiratory outcome measures

In the multivariate model (after adjusting for atopy and smoking) work-related upper respiratory symptoms due to spice were strongly associated with garlic allergen exposures (OR 2.32, CI 1.06-5.05, $p=0.035$) when comparing upper versus lower tertile exposure groups ($>0.235 \mu\text{g}/\text{m}^3$ versus $<0.066 \mu\text{g}/\text{m}^3$). General work-related lower respiratory asthma symptoms (WRLRS) were more strongly associated with endotoxin (OR 5.20, CI 1.12-24.17, $p=0.036$) when comparing $>59.06 \text{ EU}/\text{m}^3$ versus $<44.86 \text{ EU}/\text{m}^3$ tertiles and garlic allergen exposures (OR 3.22, CI 1.01-10.25, $p=0.047$) when comparing $>0.235 \mu\text{g}/\text{m}^3$ versus $<0.066 \mu\text{g}/\text{m}^3$ tertiles. Slightly lower odds ratios were observed for WRLRS due to spice dust for endotoxin exposures (OR 4.86, CI 1.04-22.63, $p=0.044$) whereas a borderline association was observed with garlic allergen exposures (OR 3.11, CI 0.97-9.95, $p=0.056$) when comparing upper versus lower tertiles.

3.2.9 Multivariate conditional logistic regression model of environmental factors associated with respiratory outcome measures

OUTCOME	PARTICULATE MASS	ENDOTOXIN CONCENTRATION	GARLIC ALLERGEN CONCENTRATION
	High vs Low >3.78 vs <1.18 mg/m ³	High vs Low >59.06 vs <44.86 EU/ m ³	High vs Low >0.235 vs <0.066 µg/m ³
	OR (95%CI)	OR (95%CI)	OR (95%CI)
WRURS	1.04 (0.46-2.33)	1.12 (0.49-2.53)	1.98 (0.93-4.18)
WRURS due to spice	1.27 (0.56-2.89)	1.31 (0.57-2.99)	2.32 (1.06-5.05)*
WRLRS	2.90 (0.78-10.70)	5.20 (1.12-24.17)*	3.22 (1.01-10.25)*
WRLRS due to spice	2.80 (0.75-10.37)	4.86 (1.04-22.63)*	3.11 (0.97-9.95)
Garlic specific IgE	1.73 (0.55-5.46)	1.09 (0.36-3.34)	1.37 (0.53-3.58)
Chili pepper specific IgE	0.27 (0.04-1.60)	1.83 (0.14-23.77)	0.30 (0.06-1.44)
Wheat specific IgE	0.72 (0.16-3.20)	4.20 (0.41-43.04)	0.82 (0.23-2.92)
At least one spice dust allergen specific IgE	2.07 (0.65-6.57)	1.35 (0.44-4.09)	1.64 (0.63-4.28)
FEV ₁ /FVC ratio (<0.7)	0.61 (0.09-4.19)	1.54 (0.15-16.30)	0.31 (0.07-1.45)
No. with FEV ₁ increase ≥12% and ≥200ml post-bronchodilator	0.31 (0.03-2.98)	1.89 (0.20-17.95)	2.58 (0.28-23.44)
Baseline FE _{NO} >15ppb	1.03 (0.44-2.44)	1.40 (0.58-3.40)	0.71 (0.33-1.51)
Baseline FE _{NO} >50ppb	0.88 (0.21-3.75)	2.53 (0.48-13.37)	1.38 (0.32-5.92)
Across-shift change FE _{NO} >10%	2.23 (0.78-6.34)	1.42 (0.54-3.71)	2.06 (0.81-5.22)
Across 24-hour period change FE _{NO} >10%	1.75 (0.66-4.66)	1.83 (0.70-4.78)	1.17 (0.51-2.65)

Note: *p<0.05; CI: confidence interval; WRURS: work-related upper respiratory symptoms; WRLRS: work-related lower respiratory symptoms; FE_{NO}: fractional exhaled nitric oxide; OR: Odds ratios derived using symptom and respiratory outcome odds in low exposure work category as reference category and are adjusted for atopy and smoking status.

3.2.10 Allergic sensitisation associated with respiratory outcome measures

The unadjusted logistic regression model illustrating the association between IgE specific sensitisation and respiratory outcome measures is outlined in Table 3.2.10.

A strong positive association was demonstrated for garlic sensitisation and general work-related lower respiratory symptoms (WRLRS) (OR 4.32, CI 1.71-10.89, $p=0.002$), WRLRS due to spice dust (OR 4.67, CI 1.83-11.89, $p=0.001$) and probable asthma based on FE_{NO} measurements >50 ppb (OR 5, CI 1.48-16.88, $p=0.01$). A similar association was demonstrated for garlic sensitisation and chronic obstructive pulmonary disease (FEV_1/FVC ratio <0.7) (OR 4.87, CI 1.13-20.90, $p=0.03$). Stratified by atopy, a stronger association was observed for non-atopic workers with WRLRS due to spice (OR 6.37, CI 1.20-33.75, $p=0.029$) compared to atopic workers (OR 3.71, CI 1.09-12.61, $p=0.035$) (data not shown).

Sensitisation to chili pepper was even more strongly associated with reversible airflow obstruction (FEV_1 increase $\geq 12\%$ and ≥ 200 ml post-bronchodilator) (OR 10.92, CI 1.66-71.85, $p=0.01$), raised FE_{NO} measurements >15 ppb (OR 5.16, CI 1.03-25.73, $p=0.04$) as well as FE_{NO} measurements >50 ppb suggestive of asthma among spice mill workers (OR 23.93, CI 5.24-109.25, $p<0.001$). A strong association was also demonstrated for chronic obstructive pulmonary disease (FEV_1/FVC ratio <0.7) (OR 15.6, CI 2.88-84.31, $p=0.001$) and chili pepper sensitisation.

A positive association was also demonstrated for wheat sensitisation and FE_{NO} measurements >50ppb suggestive of asthma (OR 6.4, CI 1.64-24.98, p=0.008), as well as for chronic obstructive pulmonary disease (OR 7.5, CI 1.56-36.04, p=0.01).

In this study chili pepper sensitisation was more strongly associated with probable asthma defined by FE_{NO} >50 ppb (OR 23.93, CI 5.24-109.25, p<0.001) than for those workers sensitised to occupational allergens wheat (OR 6.4, CI 1.64-24.98, p=0.008) or garlic (OR 5, CI 1.48-16.88, p=0.01), as well as more prevalent (56%). A similar pattern was also observed for bronchial reversibility (OR 10.92, CI 1.66-71.85, p=0.013) and chili pepper sensitisation. After adjusting for atopy the strong association between chili pepper sensitisation and probable asthma (FE_{NO} >50 ppb) persisted although the odds ratio was slightly reduced (OR 10.83, CI 2.27-51.70, p=0.003) (data not shown).

Atopic workers sensitised to chili pepper allergen demonstrated a stronger association with chronic obstructive pulmonary disease (FEV₁/FVC ratio <0.7) (OR 16.8, CI 2.25-125.32, p=0.006) than atopic workers sensitised to garlic (OR 10.35, CI 1.08-99.38, p=0.043) or wheat allergen (OR 7.65, CI 1.13-51.83, p=0.037) (data not shown).

Interestingly no associations were observed between specific IgE sensitisation and longitudinal changes in FE_{NO} levels, across the work-shift and over a 24-hour period.

Table 3.2.10 IgE specific sensitisation associated with work-related symptoms, lung function and FE_{NO} levels (n = 150)

OUTCOME	No. (%) n=150	No. (%) n=67	No. (%) n=29	No. (%) n=9	No. (%) n=14	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
	overall	atopy	garlic	chili	wheat	atopy	garlic	chili	wheat
WRURS	71 (47%)	31 (46%)	15 (52%)	4 (44%)	8 (57%)	0.93 (0.49-1.76)	1.24 (0.55-2.80)	0.88 (0.23-3.43)	1.54 (0.51-4.69)
WRURS due to spice	64 (43%)	28 (42%)	13 (45%)	3 (33%)	8 (57%)	0.94 (0.49-1.80)	1.11 (0.50-2.52)	0.66 (0.16-2.73)	1.90 (0.63-5.80)
WRLRS	26 (17%)	14 (21%)	11 (38%)	3 (33%)	5 (36%)	1.56 (0.67-3.65)	4.32 (1.71-10.89)*	2.56 (0.60-11.00)	3.04 (0.93-9.98)
WRLRS due to spice	25 (17%)	14 (21%)	11 (38%)	3 (33%)	5 (36%)	1.73 (0.73-4.11)	4.67 (1.83-11.89)*	2.70 (0.63-11.63)	3.22 (0.98-10.61)
FEV ₁ /FVC ratio <0.7	8 (5.6%)	5 (8%)	4 (15%)	3 (37%)	3 (23%)	2.02 (0.46-8.80)	4.87 (1.13-20.90)*	15.6 (2.88-84.31)*	7.5 (1.56-36.04)*
No. with FEV ₁ increase ≥12% and ≥200ml post-BD	6 (4%)	2 (3%)	2 (7%)	2 (25%)	2 (15%)	0.57 (0.10-3.22)	2.24 (0.39-12.91)	10.92 (1.66-71.85)*	5.73 (0.94-34.85)
FE _{NO} >15 ppb	64 (43%)	39 (58%)	17 (59%)	7 (78%)	9 (64%)	3.23 (1.64-6.35)*	2.23 (0.98-5.09)	5.16 (1.03-25.73)*	2.65 (0.84-8.33)
FE _{NO} >50 ppb	12 (8%)	11 (16%)	6 (21%)	5 (56%)	4 (29%)	16.11 (2.02-128.30)*	5 (1.48-16.88)*	23.93 (5.24-109.25)**	6.4 (1.64-24.98)*
Across-shift change FE _{NO} >10%	35 (23%)	16 (24%)	7 (24%)	2 (22%)	2 (14%)	1.06 (0.49-2.26)	1.06 (0.41-2.73)	0.93 (0.18-4.72)	0.52 (0.11-2.44)
Across 24-hour period change FE _{NO} >10%	40 (27%)	19 (28%)	7 (24%)	1 (11%)	1 (7%)	1.17 (0.56-2.41)	0.85 (0.33-2.17)	0.33 (0.04-2.70)	0.19 (0.02-1.51)

Note: *p<0.05; **p<0.001; % Expressed relative to number (n); CI: confidence interval; OR: each odds ratio is a separate unadjusted regression model for age, gender and smoking status. WRURS: work-related upper respiratory symptoms; WRLRS: work-related lower respiratory symptoms; FE_{NO}: fractional exhaled nitric oxide. The logistic model for FE_{NO} was based on FE_{NO} cut-off points >15ppb (median of the baseline pre-shift FE_{NO} levels) and >50ppb (probable asthma) for analyses.

Chapter 4

Discussion

This is the first detailed epidemiological study of spice mill workers documenting excessive exposure to spice dust containing garlic allergens associated with allergic respiratory disease. Various clinical end-points of allergic respiratory disease were used to demonstrate the consistency of the patterns observed.

In this study the prevalence of work-related upper respiratory symptoms (WRURS) due to spice dust was 43%, very similar to what has been reported for spice grinders (49%) in Singapore (Chan et al., 1990). The prevalence of work-related lower respiratory symptoms (WRLRS) due to spice dust, suggestive of asthma, was 17%. A similar prevalence (15%) was recorded for chest tightness among spice factory workers in Croatia (Zuskin et al., 1988b). These figures in spice factory workers are higher than those reported for bakers in the Western Cape, in which 31% reported work-related ocular-nasal symptoms, but similar to those reporting work-related chest symptoms (17%) (Baatjies et al., 2009). This is likely to be due to less irritant products being handled in bakeries compared to spice plants.

The prevalence of workers sensitised to at least one occupational allergen was high (21%), with sensitisation to garlic (19%) much higher than to wheat (9%) and chili pepper (6%). IgE reactivity to multiple spice allergens has been clearly demonstrated for spice mill workers in Croatia (Zuskin et al., 1988a). The prevalence of sensitisation to chili pepper (13.3%) in Croatian workplaces was higher than that found in the current study (6%). Workers in the former study also demonstrated

sensitisation to paprika and parsnip (11.1%), pepper and tumeric (6.7%), and onion and ginger (2.2%). The prevalence of general asthma based on bronchial reversibility and fractional exhaled nitric oxide in this study was between 4-8%. However, the prevalence of probable occupational asthma ($FE_{NO} > 50$ ppb) was slightly higher for garlic (4%) compared to wheat or chili pepper (3%). Despite a higher prevalence of sensitisation to garlic, compared to chili pepper, a much higher proportion (50%) of the workers sensitised to chili had occupational asthma. A much higher prevalence (13%) of probable occupational asthma due to wheat has been reported for supermarket bakery workers (Baatjies et al., 2009). Studies of ventilatory function revealed no significant loss of lung function in chili workers exposed to airborne chili dust, although transient spirometric changes have been recorded (Lankatilake and Uragoda, 1993).

Another novel aspect of this study was the comprehensive environmental exposure assessment conducted for inhalable particulate mass, specific spice dust allergens (garlic) and endotoxin contamination of spice dust. An assay was developed for quantification of garlic allergens using antibodies of sensitised workers that had the added advantage of being more specific than antibodies produced in animals.

Exposure metrics demonstrated a wide variation in mean (geometric) concentrations of inhalable particulate 2.06 mg/m^3 (LOD-47.64), garlic allergen $0.24 \text{ } \mu\text{g/m}^3$ (0.02-43.29) and endotoxin 60 EU/m^3 (23-390) levels. The mean concentrations were relatively higher in the blending/sifting department where bulk spices were manually added into mechanical blenders (dust particulate 5.78 mg/m^3 and garlic allergen $3.71 \text{ } \mu\text{g/m}^3$) and in the packing of raw spice work areas. However, mean endotoxin (124 EU/m^3) levels were relatively higher in the milling department where dry coarse spices were ground. A stronger correlation was also found between garlic allergen and

particulate dust ($r=0.70$) than between endotoxin and particulate dust ($r=0.43$). This latter association could be due to unrefined dry coarse spices that are generally less likely to become airborne due to their weight and larger aerodynamic size and may contain higher concentrations of endotoxin since they are closer to the organic harvest source from the farm. On the other hand, garlic allergen originates from garlic flakes/powder used in spice blends that are processed and packed in dry powder form and are therefore more likely to become airborne due to their particle size and aerodynamic properties.

The detailed exposure assessment indicated that spice mill workers are at increased risk of becoming sensitised to spice allergens (garlic, chili pepper, wheat) given that the inhalable spice dust particulate levels were on average 2 mg/m^3 . This suggests that the recommended exposure limits of 10 mg/m^3 recommended by American Conference of Governmental Industrial Hygienists (ACGIH®) for inhalable particulates not otherwise specified (PNOS) are inadequate in protecting the health of exposed workers (ACGIH® 2010). The current exposures in this plant are also lower than the 3 mg/m^3 (total inhalable particulates) proposed by the Control of Substances Hazardous to Health (COSHH) regulations of the Health and Safety Executive in the United Kingdom for irritant spice dusts such as garlic, ground chilies, mustard (HSE, 2001). However, the guideline does stipulate that exposure to spice dusts, identified as respiratory sensitisers, should be reduced as low as reasonably practical. Reducing exposure to safe levels remains, however, quite difficult in field practice, since the threshold level (or dose) of an agent that can elicit sensitisation and respiratory reactions remains largely uncertain (Moscatto et al., 2008). The Health Council of the Netherlands has made the precautionary assumption that, in the event of continued exposure, almost all sensitised workers will ultimately develop allergic

respiratory disorders (Rijnkels et al., 2008). The current study clearly demonstrated that inhalable particulate dust levels of even 2 mg/m^3 are not protective, especially with peak exposures ranging up to 47.64 mg/m^3 . There are currently no health based occupational limits for endotoxin. However, our data suggest that workers exposed to greater than 60 EU/m^3 , which is the mean exposure of this study group, have a fivefold measured risk of lower respiratory asthma-related symptoms when compared to those exposed to $<45 \text{ EU/m}^3$. This level is within the range of exposures reported by other studies to cause work-related asthma in other occupational settings (Singh et al., 2010).

In this study the prevalence of allergic rhinitis (symptoms associated with sensitisation) specifically due to garlic allergen (9%) was much higher than to wheat (5%) and chili pepper (2%). These proportions, however, are at the lower end of the range of prevalences reported for occupational allergic rhinitis in the food industry of between 3% and 60% (Gill et al., 2002). This wide variation in prevalence is highly dependant on the exposure environment and the level of exposure in a particular workplace (Moscato et al., 2008). It is likely that with this high prevalence of allergic rhinitis a proportion will go on to develop work-related asthma as has been demonstrated in previous studies of workers exposed to high-molecular-weight sensitisers (Malo et al., 1997).

One of the novel findings of this study was the use of both fractional exhaled nitric oxide (FE_{NO}) measurements as well as spirometry to assess the presence of asthma and chronic obstructive pulmonary disease. Spirometry demonstrated airway obstruction ($\text{FEV}_1 < 80\%$ predicted) in 13% of workers and 6% with evidence of

chronic obstructive pulmonary disease ($FEV_1/FVC < 70\%$). Furthermore, between 4% and 8% had evidence of asthma based on significant airflow reversibility (post-bronchodilator) or the presence of airway inflammation ($FE_{NO} > 50$ ppb) respectively. The latter test proved to be more sensitive in identifying individuals with probable asthma. The true prevalence of asthma might have been underestimated because non-allergic bronchial hyperresponsiveness was not assessed by methacholine challenge test PC_{20} (Caldeira et al., 2006).

Other studies showed that asthma could be identified in subjects with $FE_{NO} > 46$ ppb and mild to moderate asthma could be ruled out in individuals with $FE_{NO} \leq 12$ ppb measurements (Schneider et al., 2009). The findings of this study therefore suggest that both acute and chronic obstructive pulmonary disease is present in workers exposed to spice. This is consistent with the findings of studies by Zuskin *et al.* among spice workers in Croatia (Zuskin et al., 2000).

In this study the major determinants of airway inflammation associated with asthma as measured by baseline pre-shift FE_{NO} was sensitisation to occupational allergens chili pepper and garlic, aside from atopy and smoking in the univariate models. Since chili pepper ($r=0.32$) was more strongly correlated with FE_{NO} than garlic ($r=0.20$), in the final multivariate model only chili pepper persisted as a strong determinant ($\beta=0.47$) similar to smoking ($\beta=-0.47$) and more so than atopy ($\beta=0.41$). Atopy has been consistently associated with raised FE_{NO} levels, with or without asthma as has been reported in other studies (Steenenbergh et al., 2003; Franklin et al., 2003). It is also well known that smokers exhibit strongly reduced FE_{NO} levels (Malinovschi et al., 2006). It would appear from this current study that a rise in FE_{NO} levels in workers

exposed to respiratory sensitisers could be attributable to the putative exposures experienced mainly by non-atopic non-smoking individuals. That non-smokers were twice as likely (OR=2.29) to have an increase of >10% across the work shift, is highly suggestive of such an effect in operation among these workers exposed to inhalable spice dust.

Host-related factors atopy and smoking were also strongly associated with the respiratory outcome measures in this study. Atopic workers were more likely to be sensitised to any of the occupational allergens present in the spice dust. This is consistent with studies reported in the literature that demonstrate atopy to be strongly correlated with sensitisation to high-molecular-weight (protein) allergens (Kruize et al., 1997). Atopic workers were also more likely to have elevated FE_{NO} levels suggestive of asthma (OR=16) in this study. Previous studies have also demonstrated that the risk for allergen specific sensitisation and asthma is modified and increased by the workers' atopic status, with atopics having a higher risk among similarly exposed individuals (Schlünssen et al., 2004; Jeebhay and Quirce, 2007). Although no association was observed between IgE sensitisation to the occupational allergens and smoking status, smokers were more likely to present with as general work-related upper (OR=1.99) and lower (OR=2.61) respiratory symptoms as well as work-related upper respiratory symptoms (WRURS) due to spice dust (OR=2.31). This association between smoking and respiratory symptoms has also been reported in previous studies on spice workers in Croatia (Zuskin et al., 1993; Zuskin et al., 2000). Cumulative smoking has also been associated with a higher cough threshold to capsaicin among workers chronically exposed to hot chili peppers when challenged with capsaicin aerosol (Blanc et al., 1991).

The strength of the current study lies in the fact that exposure-response relationships were observed with actual levels of garlic allergen and endotoxin levels. There is increasing evidence that exposure to endotoxins has a synergistic relationship with allergy and asthma in individuals with high allergen exposures (Singh et al., 2010). While general inhalable dust particulate concentration did not demonstrate any associations with the respiratory outcomes, workers exposed to high garlic allergen concentrations (>0.235 versus $<0.066\mu\text{g}/\text{m}^3$) (OR=2.3) were more likely to present with work-related upper respiratory symptoms (WRURS) due to spice dust. Furthermore, workers exposed to high endotoxin (>59.06 versus <44.86 EU/ m^3) (OR=5.2) and garlic allergen levels (>0.235 versus $<0.066\mu\text{g}/\text{m}^3$) (OR=3.2) were more likely to present with general asthma-related respiratory symptoms (WRLRS). These high dust levels were generally found in the blending/sifting and packing areas of the spice mill. The findings of this study are consistent with studies reported among factory workers in Croatia exposed to spice dust (Zuskin et al., 1988a; Zuskin et al., 1988b).

The strong associations observed between IgE mediated sensitisation and asthma outcomes suggest a dominant immunological basis for the obstructive lung disease in these spice mill workers. Work-related lower respiratory symptoms (WRLRS) due to spice dust were strongly associated with sensitisation to garlic (OR=4.67).

Interestingly, a stronger association was observed between asthma and chili pepper sensitisation than with garlic, despite a higher prevalence of allergic respiratory disease observed with the latter in this population. This association was observed using both elevated FE_{NO} (>50 ppb) (OR=24) as well as bronchial reversibility

(OR=11) indices in relation to chili pepper sensitisation. A similar association of IgE reactivity to an array of spices (including chili pepper, paprika) that related to acute symptoms and lung function changes, has also been observed by Zuskin *et al.* (1988a). Lundberg *et al.* (1983) also found that chili and paprika dust induced a dose-dependent contraction of human segmental bronchi in vitro. Furthermore, irritant respiratory effects have also been described for chili in other studies (Uragoda, 1983). Therefore, it is likely that immunological responses to chili pepper in combination with irritant respiratory effects may lead to an enhanced airway inflammatory response resulting in asthma. A similar pattern was observed for chronic obstructive pulmonary disease (FEV₁/FVC ratio <0.7) and allergic sensitisation to chili pepper (OR=15.6) that was independent of smoking. The associations were even more pronounced in atopic workers sensitised either to chili pepper, garlic or wheat. These findings suggest that allergic asthma also leads to chronic obstructive pulmonary disease. Similar observations have also been reported in other studies of workers exposed to organic dusts in Croatian food processing industries (Zuskin *et al.*, 2000). The reasons for the stronger association observed between airway disease and chili pepper needs further investigation at a molecular level.

Our previous molecular-based studies have demonstrated a 50kDa allergen in garlic that cross-reacts with onion (Van der Walt *et al.*, 2010). In chili (whole, processed and cayenne pepper) IgE-binding proteins with molecular weights of 40kDa and 51-52kDa were also identified using IgE-immunoblotting techniques. The former was less prominent in garlic. Sensitisation patterns confirm that sensitisation to garlic and chili is highly correlated ($r=0.89$) suggesting possible cross-reactivity of allergens. Alternatively, the adjuvant effect of sensitisation to hotter spices like chili pepper,

promoting transport of molecules below a molecular mass of 70kDa, may have also contributed to the multiple sensitisations observed in these workers (Schöll and Jensen-Jarolim, 2004; Van der Walt et al., 2010). Data from other studies also suggest that sensitisation to spices is a more complex issue due to the presence of simultaneous polysensitisation to various plant profilins in pollens and foods (Jensen-Jarolim et al., 1997; Egger et al., 2006). A study among saffron workers demonstrated a significant degree of cross-reactivity between saffron and *Lolium*, *Salsola*, or *Olea* pollen through the identification of a 15.5kDa allergen present in saffron pollen and stamens which was found to have a profilinic nature (Feo et al., 1997). Schwartz *et al.* also alluded to cross-reactivity between unique allergens in fennel (67-75kDa) with components in mugwort, paprika, short ragweed and black pepper (Schwartz et al., 1997).

The spectrum of occupational asthma is expanding, with low-dose irritant mechanisms likely to account for some occupational asthma with latency (Burge, 2010). In addition to an immunological response, spices such as chili pepper, paprika, caraway, coriander leaves and seeds, cinnamon, ginger, onion, curry, and parsley also provoke direct irritant reactions in the airways (Zuskin et al., 1988a). Evidence for these irritant effects have been suggested by *in vitro* experiments that demonstrated dose-related contractile response of isolated guinea pig tracheal smooth muscle subjected to aqueous extracts of these different spices. Epidemiological studies of Sri Lankan workers, exposed to dust generated by processing spices (chili, cinnamon and cloves), have also been reported to experience work-related respiratory symptoms due to the irritant nature of the dust (Uragoda, 1992), as has been reported for spice grinders in Singapore (Chan et al., 1990). In this study a much higher overall

proportion of workers reported work-related upper respiratory symptoms (WRURS) (43%) due to spice dust in comparison to workers sensitised to any one occupational allergen (garlic, chili, wheat) (21%). A stronger association was observed between garlic sensitisation and work-related lower respiratory symptoms (WRLRS) due to spice in non-atopic workers (OR=6.37) compared to atopic workers (OR=3.71). These findings suggest that work-related upper and lower respiratory symptoms due to spice dust may have an irritant basis, although it appears to be more dominant for the upper airway effects.

A limitation of this cross-sectional study was possibly a lack of power due to sample size, but also misclassification of exposure, although NIOSH OESSM sampling method was used during stratified sampling of work processes, categorised as high, medium and low exposures, due to sufficiently dissimilar jobs within these exposure groups. Healthy worker effect was not demonstrated in this study, although it is a common limitation found in cross-sectional studies.

In conclusion, this study has demonstrated that spice mill workers exposed to inhalable spice dust with mean exposures $> 2 \text{ mg/m}^3$, containing allergens (garlic, chili pepper, wheat), are at an increased risk of developing work-related respiratory symptoms, probable asthma and chronic obstructive pulmonary disease, mediated by immunological (IgE) as well as irritant mechanisms.

Chapter 5

Recommendations

This study investigating the risk of occupational allergic respiratory disease among spice mill workers in South Africa has concluded that workers are at an increased risk of becoming sensitised to spice dust allergens following inhalation of elevated levels of spice dust ($>2 \text{ mg/m}^3$) and developing work-related respiratory disease.

In the light of above, the following measures have been proposed to prevent the development of further morbidity associated with spice dust exposure.

Firstly, *regulatory exposure standards* for spice allergens should be developed in the long-term since none currently exist internationally. This requires standardisation of immunoassays for the evaluation of allergen exposure that can be implemented by most laboratories. In the mean time the most practicable strategy would be to identify work areas and activities with high dust generating work processes (milling, blending/sifting, packing) and consequently high airborne spice dust exposure levels during initial risk assessment. Baseline and follow up exposure measurements can be used to assess the effectiveness of local extraction ventilation systems using particulate as a proxy for spice allergen (garlic) levels (since a high degree of correlation exists between these two measures). Environmental garlic allergen exposure would be process specific and be associated with the production of particular spice mixtures, but overall, garlic is generally present in work processes and can be considered generalised. While assays determining endotoxin concentration levels have achieved a greater level of standardisation, worldwide no international

exposure standards exist currently. The Dutch Expert Committee on Occupational Standards (DECOS) is currently reviewing the occupational exposure limits (OEL) for endotoxins and it is likely that a limit of between 90 and 135 EU/m³ will be proposed (DECOS 2009).

Compliance within the minimum requirements as stipulated by the Occupational Health and Safety Act, 1993 (Act No. 85 of 1993), including regulations as promulgated, is required in South Africa. No occupational exposure limit is assigned to particulates not otherwise specified (PNOS) that would include spices, herbs and mixtures thereof, with the current suggested recommended exposure limits of 10 mg/m³ that still prevail. Since these agents are biologically active, this exposure standard is inadequate in protecting the health of exposed workers. It is therefore recommended that employers strive to minimise dust particulate exposure levels as low as reasonably practical and use a benchmarking approach for ongoing further improvements in dust control. One feasible benchmark limit may for practical purposes be the threshold of upper respiratory irritation reported by workers in the particular spice plant.

Secondly, *workplace interventions and control measures* need to be implemented to reduce the exposure levels of spice dust particulate. These should include process separation or enclosure and the use of local extraction ventilation (LEV) systems to processes and equipment. Some practical suggestions include:

- a down draft or elevated side draft slot hood system installed into countertop
- round smooth steel ductwork with a minimum transport velocity of 800-900 meters per minute

- an enclosure local extraction ventilation (LEV) discharge system during milling and discharging processes of raw spice product.
- container bins configured with tight-fitting lids will also reduce spice dust emissions into the workplace.

The use of a type FFP2 respirator (with a protection factor of 10) with proper fit testing will be required in the interim in all areas with elevated dust exposures.

Workplace practices such as broom sweeping especially in the blending and packing gantry areas should be prohibited and vacuum cleaners or wet mopping should be promoted. Workers should be encouraged to vacuum their clothing (if contaminated with spice dust) using a vacuum equipped with a HEPA filter and special laundry facilities should be provided for work clothing so that the clothes remain on the premises.

Thirdly, ongoing *industrial hygiene and medical surveillance* is required to assess the effectiveness of interventions in reducing the risk of allergy and asthma. Exposure monitoring of total dust particulate as opposed to allergen levels is a realistic exposure metric to measure (particulate dust and airborne allergen garlic were strongly correlated). Medical surveillance programmes also have an important role to play. Medical surveillance programmes should include a baseline screening entry questionnaire, clinical examination, spirometry and tests for allergic sensitisation to garlic (as sensitisation was highly correlated with the other allergens) using skin prick test of allergen extract or allergen specific IgE in serum. Periodical surveillance should be done on an annual basis using a questionnaire and tests for allergic sensitisation. Where these activities indicate evidence of possible work-related

respiratory disease, additional tests (immunological tests for a larger panel of spices and pollens, serial peak expiratory flow measurements, spirometry, fractional exhaled nitric oxide measurements) can be used to confirm the presence of allergic rhinitis or occupational asthma in individual cases.

The following guidelines could be used to deal with abnormal results obtained from medical screening, surveillance and individual case management:

- Asthmatics sensitised to occupational allergens should change to work areas away from the production area (blending/sifting, packing, weighing, milling) and avoid further exposure to spice dust.
- Asthmatics without sensitisation to occupational allergens should be relocated to less exposed spice mill tasks outside the production area.
- Spice mill workers with rhinitis and sensitisation should be investigated closely and relocation to less exposed tasks outside the production area should be considered.
- Spice mill workers sensitised to occupational allergens, but without respiratory symptoms, should be re-examined annually.
- Spice mill workers with rhinitis only, but without sensitisation to occupational spice allergens, may not warrant re-examination unless their symptoms worsen or they develop asthma.

Finally, *education and training* programs for employers, workers and occupational health service providers are also needed. Essential components of such programs include importing knowledge of allergic respiratory disease end-points to all stakeholders as well as promoting competence and skills of health service providers

to conduct medical surveillance. Information and training of workers and supervisors should include details on dust control procedures and precautionary measures to follow during the handling of spice products.

Finally, a number of unanswered questions of importance remain that need to be addressed in future research. A detailed exposure characterisation of chili pepper exposure in spice mill settings and its relationship to work-related respiratory symptoms, allergic health outcomes and exploration of the underlying pathophysiological mechanisms involved need further investigation. The association between allergic reactions to eating spicy foods and inhalant adverse reactions in relation to asthma is another end-point that should be addressed in future research. Future studies should look closer into the relationship between pollens and specific IgE sensitisation to spices using component resolved diagnostics to study co-reactivity patterns and ELISA inhibition techniques for cross-reactive allergens. In this way pan-allergens could be identified. Furthermore, characterisation of the molecular nature of aerosolised spice allergens, including the sequencing of the proteins, is an additional area of future research.

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Appendices

- Appendix A: Published manuscript: Van der Walt A, Lopata AL, Nieuwenhuizen NE, Jeebhay MF: Work-related allergy and asthma in spice mill workers - the impact of processing dried spices on IgE reactivity patterns. *Int Arch Allergy Immunol* 2010;152:271-278.
- Appendix B: Ethics approval
- Appendix C: Briefing document Work-related Allergy and Asthma to Spices in the Spice Mill
- Appendix D: Consent for Determinants of Occupational Allergy to Spices in a Spice Mill
- Appendix E: Personnel distribution and Environmental sampling
- Appendix F: Respiratory Questionnaire Occupational Allergy among Spice Workers
- Appendix G: Lung function pre-test questionnaire spice mill study
- Appendix H: Lung function test data collection sheet spice mill study
- Appendix I: FE_{NO} pre-test data collection sheet Occupational Allergy to Spices in a Spice Mill
- Appendix J: FE_{NO} data collection sheet Occupational Allergy to Spices in a Spice Mill
- Appendix K: Guideline for assessing and managing medical screening results
- Appendix L: Medical report of results
- Appendix M: Photographs of spice mill production area

Appendix A

Published manuscript

Van der Walt A, Lopata AL, Nieuwenhuizen NE, Jeebhay MF:

“Work-related allergy and asthma in spice mill workers - the impact of processing dried spices on IgE reactivity patterns”.

Int Arch Allergy Immunol 2010;152:271-278.

Work-Related Allergy and Asthma in Spice Mill Workers – The Impact of Processing Dried Spices on IgE Reactivity Patterns

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Key Words

Work-related allergy · Allergy · Asthma · Garlic · Processed allergens · Spices

Abstract

Background: Three spice mill workers developed work-related allergy and asthma after prolonged exposure to high levels (>10 mg/m³) of inhalable spice dust. Patterns of sensitization to a variety of spices and putative allergens were identified. **Methods:** Work-related allergy and asthma were assessed on history, clinical evaluation, pulmonary function and fractional exhaled nitric oxide. Specific IgE reactivity to a range of common inhalant, food and spice allergens was evaluated using ImmunoCAP and allergen microarray. The presence of non-IgE-mediated reactions was determined by basophil stimulation (CAST-ELISA). Specific allergens were identified by immunoblotting to extracts of raw and dried processed garlic, onion and chili pepper. **Results:** Asthma was confirmed in all 3 subjects, with work-related patterns prominent in worker 1 and 3. Sensitization to multiple spices and pollen was observed in both atopic workers 1 and 2, whereas garlic and chili pepper sensitization featured in all 3 workers. Microarray analysis demonstrated prominent profilin reactivity in atopic worker 2. Immunoblotting demonstrated a 50-kDa cross-reactive allergen in garlic and on-

ion, and allergens of approximately 40 and 52 kDa in chili pepper. Dry powdered garlic and onion demonstrated greater IgE binding. **Conclusions:** This study demonstrated IgE reactivity to multiple spice allergens in workers exposed to high levels of inhalable spice dust. Processed garlic and onion powder demonstrated stronger IgE reactivity than the raw plant. Atopy and polysensitization to various plant profilins, suggesting pollen-food syndrome, represent additional risk factors for sensitizer-induced work-related asthma in spice mill workers.

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Introduction

The food industry employs a large proportion of workers exposed to potential allergens capable of causing occupational allergies and asthma [1]. Among consumers reporting food allergies, affecting 2% of the adult population in the industrialized world, spice allergy represents 2% of such cases [2]. Since spices are derived from plants, they have allergenic potential due to the bioactive ingredients present in processed vegetable dusts capable of inducing symptoms ranging from mild local to severe systemic allergic reactions [3]. Workers in the spice-related industry are exposed to a variety of different respi-

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ratory sensitizers that may cause sensitization through inhalation or skin contact. Inhalation of spice dust has the potential to cause respiratory allergies such as rhinoconjunctivitis and asthma, contact dermatitis and occasionally anaphylaxis. Furthermore, irritant reactions in addition to these allergic responses in workers handling spices have also been reported [4]. Occupational asthma has been reported to a range of spices including garlic, onion, paprika, mace and coriander [5, 6].

Garlic (*Allium sativum*) belongs to the Alliaceae family (formerly Liliaceae), with the first report of garlic-induced asthma dating back to 1940, when Henson [7] described an atopic foreman with ragweed pollinosis whose asthmatic symptoms disappeared after the garlic 'powder' was replaced with 'kernels'. Inhalation-related garlic allergy has since been reported in different occupational settings including food preparation and catering, sausage making, harvesting and storing of garlic bulbs, spice manufacturing, as well as packing and selling of spices [8–11]. While garlic (*A. sativum*) is known to be one of the most frequent causes of dermatitis of the fingertips in caterers [12], occupational airborne allergic contact dermatitis with concurrent type 1 allergy has also been described due to garlic dust exposure [13]. Although considered rare, reports of allergic reactions after the ingestion of foods belonging to the Liliaceae family have been described [10, 14]. Other members of this family such as onion, leek and asparagus have also been reported to cause allergic reactions among exposed individuals. Immunological evidence of cross-reactivity between garlic and other related members of the Liliaceae family such as onion in patients with occupational asthma has also been described [6, 10]. Work-related respiratory symptoms in chili grinders have also been reported, although it was considered to be probably due to the irritant nature of the dust [15].

Most of the studies on occupational asthma caused by inhalation of garlic dust, have investigated IgE reactivity patterns only to a selected spice [7, 9–11, 16, 17], whereas in spice mills, spice workers have concurrent exposures to multiple spices during work activities. An added complexity in identifying putative allergens in spice mill workers is the wide variation of spice blends produced that is dependent on local availability, geographic tradition and recipes of popular manufacturers. Recent reports of a number of cases of work-related asthma from a spice mill prompted detailed investigation of 3 index cases by analysing their immune responses to an extensive range of spices and to identify the allergens responsible for their allergic symptoms.

Methods

Pulmonological Assessment

Work-related allergy and asthma were assessed on history and clinical evaluation using a standard respiratory questionnaire adapted for the spice dust work environment [18]. Spirometry and assessment of reversible airway obstruction were done according to guidelines of the American Thoracic Society/European Respiratory Society [19]. Work-relatedness of symptoms was determined by serial peak expiratory flow rate monitoring 4 times daily at work (2 weeks), away from work (2 weeks) and back at work (2 weeks). A portable fractional exhaled nitric oxide (FENO) sampling device (NIOX MINO[®] Airway Inflammation Monitor, Aerocrine AB, Solna, Sweden) was used to obtain serial FENO concentrations across the work shift [20].

Immunological Assessment

Specific IgE reactivity to a range of common inhalant and food allergens as well as 31 different spices was evaluated using ImmunoCAP (Phadia, Uppsala, Sweden). A cut-off point of <0.1 kU/l was used as the lowest limit for detecting specific IgE antibodies. The list of spices was compiled after obtaining an inventory of raw ingredients with allergenic potential used in the spice mill for which a specific ImmunoCAP test was available. Skin prick tests used a battery of common inhalant allergens (ALK-Albello) including grass pollens, house dust mites, cockroaches, cat, dog and various moulds. Atopy was defined as a positive skin prick test to common inhalant allergens. Specific IgE to defined natural and recombinant pollen and food allergens was quantified by allergen microarray (ISAC version CRD-79b, VBC-Genomics, Vienna, Austria) according to previously described methods [21]. Allergen-induced activation of basophils by preservatives (sodium benzoate and K-metabisulphite) was determined using the CAST-ELISA (Bühlmann, Switzerland) for sulphidoleukotriene release according to the manufacturer's manual.

Garlic Extract and Immunoblotting

Extracts were prepared from raw onion and garlic as well as garlic powder, onion flakes, chili pepper, whole chili and cayenne pepper freshly collected from the spice mill. Homogenized raw onion and garlic as well as spices were extracted in phosphate-buffered saline overnight at 4°C. The spice extracts were then centrifuged to remove large particulate matter. The extracts were separated by electrophoresis on 5–16% sodium dodecyl sulphate polyacrylamide gradient gels and transferred onto a polyvinylidene difluoride membrane (Hybond-PVDF, Amersham). Membranes were incubated with patients' sera, and IgE-binding proteins were detected using alkaline-phosphatase-labeled monoclonal antihuman IgE antibody (Sigma, USA) with the chromogenic substrate 5-bromo-4-chloro-3-indolyl phosphate/nitroblue tetrazolium (Sigma, USA).

Results

History and Clinical Examination

All 3 workers reported work-related rhinitis and asthma symptoms that developed within 6–8 months of ex-

posure to various spice blends (table 1). There was, however, no history of food or spice allergy due to ingestion in any of these workers. Although garlic powder dust was the main spice reported by the workers to be causing their symptoms, other spice blends containing onion, cayenne and chili pepper as well as soya were implicated.

The occupational history indicated that aside from the variety of spices belonging to different families and species, spice mill workers were also exposed to grain flour dust (wheat and maize) as well as preservatives (sodium benzoate and K-metabisulphite). The production area of the spice mill is a general area where all the processing activities such as blending and packing of spice product are conducted except for milling, which occurs in a separate department. Dry materials such as peppercorns, coriander, paprika and chili peppers (*Capsicum annuum*) are crushed and ground in this milling area. Only hot peppers as opposed to bell peppers are used in this plant. Garlic is also used in a dried form as flakes, powder or granules during the blending of spice in the spice mill. An independent supplier manufactures the garlic product used in the spice mill. During this manufacturing process, garlic flakes are produced by a steam heat process at 65°C for 5 h. A report from a recent industrial hygiene survey conducted in the plant revealed that the inhalable dust levels ranged from 8.7 to 29.9 mg/m³ in the blending area and from 1.0 to 26.4 mg/m³ in the packing area, indicating that the extraction ventilation system in this spice mill was dysfunctional and inadequate in reducing spice dust exposures. The specific job histories obtained from these index cases revealed that worker 1 and 2 worked as feeder operators in the blending area, feeding raw spice into mixing bins, and worker 3 was a packer of raw spice product.

Pulmonological Assessment

Spirometry results of workers 1 and 2 demonstrated mild airway obstruction with significant reversibility of FEV₁ after bronchodilator administration (table 1). Although worker 3 had normal spirometry, the methacholine challenge test was positive (PC₂₀ = 2.3 mg/ml). A chest radiograph revealed no evidence of allergic alveolitis in all 3 workers. Serial peak expiratory flow rate measurements confirmed a work-related pattern in workers 1 and 3, with an OASYS work effect index for asthma symptoms of 2.75 observed in worker 3 (a value of <2.5 is considered to have a low probability of being work-related). FENO measurement was distinctly raised (>50 ppb) in worker 2 across the entire shift.

Immunological Assessment

Skin prick testing to a standard panel of common aeroallergens revealed that only workers 1 and 2 were atopic (table 1). Garlic and chili pepper sensitization featured in all 3 workers. Worker 2 demonstrated very high specific IgE reactivity to garlic (208 kU/l) and chili pepper, and was also sensitized to most of the spices tested, including grain flours. Worker 1 demonstrated moderate reactivity to garlic, chili pepper and wheat, and was sensitized to several other spices as well. Worker 3 showed low levels of specific IgE antibody (<0.7 kU/l) to garlic and chili pepper only. All 3 workers demonstrated sensitivity to either one or both preservatives. High specific IgE reactivity to birch pollen and moderate levels to mugwort pollen was observed for worker 2, whereas worker 1 showed relatively low levels of IgE reactivity to these pollens.

Microarray analysis demonstrated that worker 2 reacted to a variety of plant profilins from birch tree (Bet v 2), olive and palm tree, bermuda and timothy grass, sunflower and other weeds as well as the latex (Hev b 8) profilin (table 2). In addition, worker 2 also had elevated specific IgE to peach lipid transfer protein (Pru p 3). Worker 1 only displayed reactivity to perennial rye (Lol p 1) and timothy grass (Phl p 1, Phl p 2, Phl p 5, Phl p 6) allergens, none of which are profilins. Worker 3 did not recognise any of the allergens tested, confirming the non-atopic status observed on skin prick testing. All 3 workers displayed no reactivity to bromelain, regarded as a marker for cross-reactive carbohydrate determinants.

Sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) demonstrated a dominant protein of approximately 50 kDa for garlic powder and onion flakes, while a 40-kDa protein was the most prominent in the extract of chili pepper (fig. 1). Immunoblotting demonstrated a similar pattern of allergen recognition in workers 1 and 2 with the major IgE-binding protein for both garlic and onion extracts at 50 kDa, the garlic allergen showing the stronger band. Furthermore, greater IgE reactivity was demonstrated to the powdered form compared to the raw form for both garlic and onion. In chili (whole, processed and cayenne pepper), IgE-binding proteins with molecular weights of 51–52 and 40 kDa were recognised by both workers 1 and 2. IgE binding was not observed in worker 3 (data not shown), probably due to the very low levels of specific IgE as determined by ImmunoCAP.

Table 1. Clinical, pulmonological and immunological assessment of spice mill index cases with work-related asthma

		Worker 1	Worker 2	Worker 3
	Age:	28 years	29 years	28 years
	Gender:	male	male	female
	Smoking status:	smoker	non-smoker	non-smoker
Exposure history	Exposure duration	2 years	2 years	8 years
	Job type	feeder operator	feeder operator	packer
	Spice causing symptoms	garlic, onion, chili pepper	garlic, onion, soya	garlic, black pepper, cayenne pepper
Work-related symptoms	Asthma-related	yes (6 months)	yes (8 months)	yes (2 months)
	Ocular-nasal	yes	yes	yes
Pulmonological assessment	Chest radiograph	NAD	NAD	NAD
	Spirometry:			
	- FEV ₁ pre-BD/post-BD, ml	3,430/3,750	2,890/3,530	2,820/2,690
	- FVC pre-BD/post-BD, ml	4,440/4,690	4,740/5,060	3,070/3,160
	Methacholine challenge test PC ₂₀ , mg/ml	N/A	N/A	2.3 (positive)
	Work-related changes on serial PEFR	yes	N/A	yes
	FENO serial, ppb:			
	day 1 pre-shift/post-shift/day 2 pre-shift	22/22/22	84/76/65	17/13/-
Immunological assessment (in vivo)	Skin prick test common aeroallergens	positive	positive	negative
Immunological assessment (in vitro)	Specific IgE, kU/l			
Pollens				
<i>Betula verrucosa</i>	common silver birch	0.88	>100	<0.10
<i>Artemisia vulgaris</i>	mugwort	1.45	35.70	<0.10
Spice family				
Alliaceae	garlic	2.37	208.00	0.63
	onion	2.05	33.00	<0.10
Solanaceae	chili pepper	0.89	53.10	0.51
	paprika	0.68	2.89	<0.10
Zingiberaceae	cardomon	1.23	6.60	<0.10
	ginger	0.89	4.71	<0.10
Lamiaceae	marjoram	1.90	5.31	<0.10
	oregano	0.52	2.23	<0.10
	sage	0.86	1.42	<0.10
	thyme	<0.10	3.24	<0.10
	mint	0.29	0.81	<0.10
	basil	0.12	0.38	<0.10
Brassicaceae	mustard white	0.91	4.09	<0.10
Apiaceae	fennel	1.33	6.29	0.12
	anise	0.46	2.75	<0.10
	celery	0.76	9.26	<0.10
	caraway	0.55	1.34	<0.10
	coriander	0.45	1.75	<0.10
	parsley	1.17	10.10	<0.10
Myrtaceae	allspice	0.12	0.52	<0.10
	cloves	0.14	0.32	<0.10
Piperaceae	black pepper	0.96	3.42	<0.10
Lauraceae	bayleaf	0.14	0.51	<0.10
	cinnamon	<0.10	0.19	<0.10
Myristicaceae	mace	1.87	8.36	<0.10
	nutmeg	0.18	0.32	<0.10
Grains	wheat	1.71	8.03	<0.10
	maize	0.97	11.80	<0.10
Soya bean	soya	2.21	7.07	<0.10
Other foods	Santa Maria curry	0.83	8.78	<0.10
	tomato	0.86	37.10	<0.10
Preservatives	CAST ELISA			
	Sodium benzoate (negative cut-off: 90 pg/ml)	260	70	140
	K-metabisulphite (negative cut-off: 40 pg/ml)	160	50	20

NAD = No abnormality detected; N/A = not applicable; PEFR = peak expiratory flow rate.

Table 2. Microarray IgE analysis of sera of spice mill index cases with work-related asthma to selected pollen and food allergens

Species name	Allergen	Function	Worker 1 IgE, kU/l	Worker 2 IgE, kU/l	Worker 3 IgE, kU/l
Tree pollen					
<i>Betula verrucosa</i> (birch)	Bet v 1	ribonuclease	<0.01	<0.01	<0.01
<i>Betula verrucosa</i>	Bet v 2	profilin	<0.01	28.10	<0.01
<i>Olea europaea</i> (olive)	Ole e 1	trypsin inhibitor	<0.01	1.37	<0.01
	Ole e 2	profilin	<0.01	25.66	<0.01
<i>Phoenix dactylifera</i> (date palm)	Pho d 2	profilin	<0.01	17.26	<0.01
Weeds					
<i>Helianthus annuus</i> (sunflower)	Hel a 2	profilin	<0.01	26.06	<0.01
<i>Mercurialis annua</i> (annual mercury)	Mer a 1	profilin	<0.01	21.48	<0.01
<i>Parietaria judaica</i> (wall pellitory)	Par j 3	profilin	<0.01	37.29	<0.01
Food					
<i>Malus domestica</i> (apple)	Mal d 1	ribonuclease	<0.01	<0.01	<0.01
<i>Prunus persica</i> (peach)	Pru p 3	lipid transfer protein	<0.01	7.38	<0.01
<i>Apis graveolens</i> (celery)	Api g 1	ribonuclease	<0.01	<0.01	<0.01
<i>Daucus carota</i> (carrot)	Dau c 1	PR-10 protein	<0.01	<0.01	<0.01
Grass					
<i>Cynodon dactylon</i> (bermuda grass)	Cyn d 12	profilin	<0.01	20.92	<0.01
<i>Lolium perenne</i> (perennial rye grass)	Lol p 1	expansin	15.42	49.17	<0.01
<i>Phleum pratense</i> (timothy grass)	Phl p 1		10.59	48.96	<0.01
	Phl p 5		22.07	14.02	<0.01
	Phl p 12	profilin	<0.01	13.30	<0.01
	Phl p 2		30.98	<0.01	<0.01
	Phl p 6		2.41	36.84	<0.01
Latex					
<i>Hevea brasiliensis</i>	Hev b 8	profilin	<0.01	17.87	<0.01
Bromelain					
<i>Ananas comosus</i>	Ana c 2	CCD marker	<0.01	<0.01	<0.01

CCD = Cross-reactive carbohydrate determinant.

Discussion

In this study, we report work-related allergy and asthma among 3 spice mill workers, likely due to garlic, onion and chili pepper sensitization after exposure to a multitude of airborne spices, with no previous history of spice or food allergy. Food allergy to Liliaceae vegetables (garlic, onion, leek and asparagus) and spices is relatively rare, but allergic reactions to garlic on ingestion and work-related asthma secondary to inhalation of garlic dust have been reported [7, 9–11, 16, 17]. Potentially fatal adverse reactions, including anaphylaxis, have also been described after the ingestion of garlic [10, 22]. In one case, anaphylaxis occurred after ingestion of young unripe garlic in a woman with a previous history of allergy to pollen and dried fruit, and food-dependent, exercise-induced ana-

phylaxis. As is the finding in this study, Falleroni et al. [11] also reported a case of work-related asthma due to garlic dust exposure in which the patient tolerated ingestion of cooked garlic and onion without symptoms. It is possible that this may have been due to either inactivation or alteration of the allergenicity of the antigen through the heating process or gastric digestive processes.

In this study, immunoblotting revealed a 50-kDa cross-reactive allergen in garlic and onion, garlic being the most prominent. Several garlic protein allergens have been identified in previous studies of allergy due to garlic. In a study by Anibarro et al. [8], two major protein bands were demonstrated at approximately 12 and 54 kDa by electrophoresis of garlic extract. The latter proved to be the major IgE-binding protein and shared similar allergenic epitopes with onion. The allergenic components of

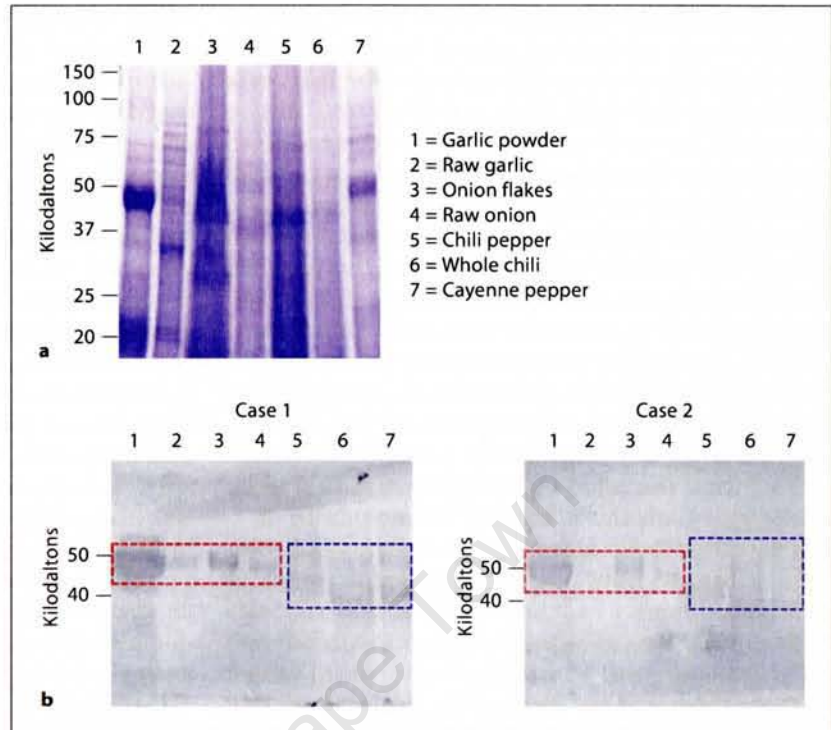


Fig. 1. Immunoblots of 2 spice mill workers with work-related asthma using spice extracts. Allergen recognition in spice mill index cases. **a** Spice extracts were electrophoresed on a 5–16% SDS polyacrylamide gel. **b** Spice extracts were transferred onto polyvinylidenedifluoride membrane. Sera from workers 1 and 2 were used to detect IgE-binding proteins. Left-sided boxes highlight IgE-binding proteins of garlic and onion and right-sided boxes indicate IgE-binding proteins of chili for worker 1 and 2.

garlic were also shown to be shared by several Liliaceae with SDS-PAGE immunoblotting when IgE-binding proteins of 12 kDa were found in young garlic, garlic, onion and leek extracts [22]. Two main IgE-binding proteins with molecular weights of 55 and 35 kDa were revealed in extracts of fresh garlic and onion, and only the 35-kDa protein showed strong IgE binding with serum from a worker with occupational asthma due to onion [6]. Alliin lyase, a 56-kDa IgE-binding protein, has recently been identified as a major garlic allergen in a group of Taiwanese patients aged 7–48 years with garlic allergy. This protein is widely distributed in other *Allium* species, namely leek, shallot, onion, and has been described as a potentially new cross-reactive allergen [16].

In chili (whole, processed and cayenne pepper), IgE-binding proteins with molecular weights of 51–52 and 40 kDa were recognised during IgE immunoblotting for both workers 1 and 2, whereas SDS-PAGE demonstrated a band of about 40 kDa as the most prominent for chili pepper extract. The particular molecular weights of these proteins, and whether they are related to the protein allergens identified for garlic and onion, can only be confirmed with the sequencing thereof. However, Schöll et al. [3] have suggested that the hotter spices, as is the case with

chili, are the more likely to act as adjuvants for sensitization by promoting transport of molecules below a molecular mass of 70 kDa. This molecular size corresponds to the size of molecules relevant for sensitization and IgE binding in spice-related allergy as observed in this study. It is possible that in addition to the dried product, an adjuvant effect may also have contributed to the multiple sensitizations observed in two of these three workers.

Another novel finding of this study is the role of processing techniques on the IgE reactivity patterns observed. One of the major allergen families that appears to lose its capacity to elicit allergic reactions in processed foods is the Bet v 1 superfamily of plant food allergens. The food matrix itself and processing procedures may be responsible for the apparent thermolability of Bet v 1 homologues in foods such as apple [23]. However, this is not so for other foods such as celery root which retains its allergenicity after cooking [24]. Recent studies of Bet v 1 have shown it to be relatively thermostable, the protein unfolding only at temperatures above 68°C [25]. Furthermore, the dry heating of food (e.g. roasting) can result in enhanced allergenicity as has been demonstrated for other plant allergens such as peanuts [26]. In this non-enzymatic reaction, called Maillard reaction, free amino groups on

proteins bind to the aldehyde or ketone groups of sugars and these glycosylated proteins can undergo further structural re-arrangements called Amadori products (important for flavour and aroma). The roasted peanut allergens have demonstrated over 100-fold increased allergenicity as well as increased stability against gastric digestion. These effects have not been previously demonstrated for dried spices, and could well be one of the effects leading to the enhanced IgE-binding reactivity of the heat dried garlic and onion flakes observed in this study as none of the workers displayed reactivity to bromelain, a known marker for cross-reactive determinants. SDS-PAGE and IgE immunoblotting demonstrated a prominent band of approximately 50 kDa for both raw and processed garlic and onion, with the garlic powder being most dominant. This suggests that this allergenic protein is cross-reactive, heat stable and enriched in the extracts after processing. Altered and enhanced allergenicity was therefore evident in both garlic and onion processed in its dried form.

In this study, worker 2 showed marked reactivity on allergen microarrays to a number of tree and weed pollens in addition to other plant-derived food allergens, mainly from the allergen protein family of profilins [27]. Patients with pollinosis often display sensitization to various plant-derived foods (class 2 food allergies). These reactions are the result of IgE cross-reactivity to profilins and lipid transfer proteins, but may also be due to high-molecular-weight glycoproteins [28]. Clinical pollen-food syndromes such as the mugwort-mustard allergy, celery-mugwort-spice allergy and the celery-birch-mugwort-spice syndrome have been previously described [29, 30]. Patients with food allergies specifically to Liliaceae (garlic, onion, leek) have also been found to have celery-mugwort-spice syndrome [31]. Birch tree (*Betula verrucosa*) profilin Bet v 2 and mugwort (*Artemisia vulgaris*) profilin Art v 4 have been identified as significant contributors to allergic reactions to pollen and plant-derived food within the celery-birch-mugwort association due to cross-reaction with celery profilin Api g 4 [32, 33]. In this study, both workers 1 and 2 were sensitized to common silver birch tree and mugwort weed pollens as well as to celery (by ImmunoCAP) and grass pollens (by microarray). Anibarro et al. [8] found that IgE binding to garlic allergens was almost completely inhibited by cross-reacting timothy grass (*Phleum pratense*) pollen extracts. However, Leitner et al. [34] investigated allergens originating from pepper (Piperaceae) and paprika (Solanaceae) and showed that IgE cross-reactivity in the celery-birch-mugwort-spice syndrome to spices other than Apiaceae is not exclusively caused by Bet v 1 homologs and/or

profilins. Worker 2 also tested positive to Pru p 3 allergen (7.38 kU/l), a lipid transfer protein from peach which is associated with sensitization to taxonomically diverse pollens [35]. While it is well known that cross-reactive pan-allergens are implicated in pollen-food syndromes, the exact role of profilins in triggering allergic symptoms is still unclear [28]. Pan allergen reactivity was clearly demonstrated for worker 2 who was sensitized to multiple plant-derived spices probably due to inhalation. In addition, profilin appeared to act as a cross-reactive pan-allergen in this worker and pollinosis may therefore pose as a risk factor in the development of spice allergy. The class 2 allergy, particularly the celery-birch-mugwort-spice association may be of importance in this worker, and the relationship between pan-allergens and garlic allergens needs further investigation at a molecular level.

In conclusion, the findings of this study suggest that spice mill workers are at increased risk of becoming sensitized to multiple spice allergens when exposed to inhalable spice dust levels of more than 1 mg/m³, suggesting that the currently recommended exposure limits of 10 mg/m³ (American Conference of Government Hygienists) for inhalable particulates not otherwise specified may be inadequate in protecting the health of exposed workers. However, the exact composition of the dust and the specific concentration of allergens present in the dust need further investigation. Furthermore, garlic and onion powder demonstrated enhanced allergenicity in the processed dry form and was more likely to become airborne. Atopy and simultaneous sensitization to various plant profilins may pose additional risk factors for sensitization to class 2 allergens and occupational asthma in these workers. Garlic, onion and chili pepper should be considered as potential allergens in spice mill workers presenting with work-related asthma and any individual exposed to aerosolized spices.

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Appendix B

Ethics approval

University of Cape Town



UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: lamees.emjedi@uct.ac.za

27 May 2008

REC REF: 179/2008

Prof MF Jeebhay
Public Health & Family Medicine

Dear Prof Jeebhay

**PROJECT TITLE: DETERMINANTS OF OCCUPATIONAL ALLERGY TO SPICES AMONG
SPICE MILL WORKERS.**

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above mentioned study.

The approval is granted for one year until 25 May 2009.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethical Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code of Federal Regulation Part 50, 56 and 312.

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

Appendix C

Briefing document

Work-related Allergy and Asthma to Spices in the Spice Mill

University of Cape Town

WORK-RELATED ALLERGY AND ASTHMA TO SPICES IN THE SPICE MILL

We are gathered here today to inform each person here that we would like to do medical surveillance on everybody as required by the Occupational Health and Safety Act, 1993.

Cases of occupational asthma have been identified over the past few years and we would like to do follow-up tests on each worker here in the Spice Mill to evaluate this problem and prevent further cases.

We aim to identify health problems such as allergy and asthma that may be related to exposure to spice dust at an early stage so as to protect your health and prevent further deterioration.

The University of Cape Town, Occupational and Environmental Health Research Unit, was asked to supervise the evaluation and thus establish a good baseline for Freddy Hirsch Group for future measurement and prevention of risk and health effects.

The following tests will be done on each person here at the Spice Mill:

- Consent form
- Questionnaire on symptoms of allergy and asthma
- Blood tests to identify if you are allergic to certain spices and general non-work allergens
- Lung function tests to see how healthy the lungs are and another test to measure airway inflammation, which is an early sign of asthma.
- The second lung test is called the ENO test. It is very important for every one to know that we will do this test on a new group of morning shift workers every week **BEFORE** you start work on Monday AND Tuesday (provided you did not work the weekend). On the Monday, you will also be tested again at the **END** of your shift just before you go home.

It is also very important that you must **not eat, drink or smoke one hour before the test**. We will systematically call everybody over the next few weeks to blow into this machine. You will know well in advance (by the Friday of the week before) when it is going to be your turn.

Other tests including questionnaires, blood pressure, weight, height measurements and blood tests will be done **during** the shift in the remainder of the same week by Sister Dawn.

Individual results will be confidential and personal information will only be released with the worker's consent should the need arise. All workers with abnormal results will be offered referral to the Occupational Diseases clinic at Groote Schuur Hospital for further evaluation. Where the disease is not considered to be work-related, they will be referred to their family practitioner for further evaluation/treatment. Should the disease be confirmed as work-related, worker's compensation claims will be submitted.

Dr Anita Schutte

Prof Mohamed Jeebhay and Sister Dawn Venter, UCT

Date: 14 Jan 2008

Appendix D

Consent

Determinants of Occupational Allergy to Spices in a Spice Mill

University of Cape Town

**UNIVERSITY OF CAPE TOWN
OCCUPATIONAL ALLERGY AMONG SPICE MILL WORKERS
FREDDY HIRSCH GROUP - 2008**

ENGLISH CONSENT FORM

Title of research project

- Determinants of Occupational Allergy to Spices in a Spice Mill

Purpose of the research

- The University of Cape Town (UCT) is conducting this important study of the allergic effects of exposure to spice dust. This study is going to be done by Dr Anita Schutte under the supervision of Prof Mohamed Jeebhay, Occupational and Environmental Health Research Unit, UCT, who is independent of the company. We will be studying each worker here at the Spice Mill. It is hoped that this study will provide greater insight into the risk factors for allergic sensitisation among Spice Mill workers and identify appropriate preventative strategies to be implemented in order to reduce the incidence of allergy and asthma among Spice Mill workers.

Description of the research project

- If you agree to participate you will be asked to complete the following tests during working time:

Complete a questionnaire

- A member of our study team will interview you in privacy to complete the questionnaire. You will be asked questions about any breathing or chest problems; current and previous employment history, working with spices and dietary history.

Blood test

- You will also be asked to undergo a blood test to check for allergies to specific spice allergens.
- Ten ml (about two teaspoons) of blood will be drawn once by a nurse.

Breathing test

- You will be asked to blow on 3 occasions into a NIOXMINO machine, which measures nitric oxide produced by the airways. This machine is used to detect if a person has allergic airway inflammation which is present in asthma or rhinitis.
- You will be asked to blow into a spirometer/lung function test machine to see how healthy the lungs are.

Confidentiality of information collected

- Your name will not appear in any reports on this study. The records of blood tests, questionnaires and breathing tests will be kept completely confidential and will be seen only by members of the study team.

Risks and discomforts of the research

From the blood tests:

- You will feel a single needle stick when the blood is taken. Sometimes a small bruise may occur from the needle stick, but this is minor and will heal quickly. The total amount of blood taken is quite small and your body will quickly replace it.

From the questionnaire and breathing tests:

- There are no risks from completing the questionnaire or performing the breathing tests.

Expected benefits to you and to others

- You will be given a written copy of all your test results along with an explanation of what they mean, unless you tell us that you do not wish to receive this. You may wish to show these to your doctor if you are having any problems. These tests will help determine if you have an allergy to spices or other substances used in the skin tests. What we learn from this study will help to protect you, and those working with spices in South Africa and other parts of the world. We will learn how best to monitor worker's health and how to reduce workers' exposure to spice allergens.

Costs to you resulting from participation in the study

- The study is offered at no cost to you. In the event a problem is discovered and you wish to be seen by a doctor for it, we can recommend to you who to see. However, the study cannot pay for these additional medical visits or treatments.

Contact person

- You may contact one of the following persons for answers to further questions about the research, your rights, or any injury you may feel is related to the study.

University of Cape Town Researchers:

Prof. Mohamed Jeebhay, Telephone No. (021) 406-6309

Dr Anita Schutte, Telephone No. (021) 4626310

University of Cape Town Research Ethics Committee:

Ms. Xolile Fula (Ethics Administrator) (021) 406-6492

PLEASE KEEP THIS INFORMATION SHEET WITH YOU FOR FUTURE REFERENCE

**UNIVERSITY OF CAPE TOWN
OCCUPATIONAL ALLERGY AMONG SPICE MILL WORKERS
FREDDY HIRSCH GROUP - 2008**

ENGLISH CONSENT FORM

STUDY/SURVEY NO. _____

Consent of the participant

I have read the information given above, or it has been read to me. I understand the meaning of this information. Sr Dawn Venter/ Dr A Schutte has offered to answer any questions concerning the study.

By signing this form, I hereby consent to participate in the study. I also understand that I am free to withdraw from the study at any time without penalty.

Documentation of the consent

One copy of this signed document will be kept together with our research records for this study. A copy of the information sheet about the study will be given to you to keep.

Printed name of participant

Signature, Mark, or Thumb Print

Interviewer's name (Print)

Signature

DATE: _____

Appendix E

Personel distribution and environmental sampling

University of Cape Town

PRODUCTION AREA

		PERSONEL DISTRIBUTION SPICE MILL					ENVIRONMENTAL SAMPLES			
		TOTAL	MORNING	AFTERNOON	TOTAL Morning and Afternoon	NIGHT	MORNING	AFTERNOON	TOTAL NUMBER OF SAMPLE	%
EXPOSURE HIGH BLENDING	Machine Operator (1 ton A)									
	Machine Operator (2 ton A)									
	Feeder (1 ton A)									
	Feeder (1 ton A)									
	Feeder (1 ton A)									
	Machine Operator (1 ton B)									
	Feeder (1 ton B)									
	Feeder (1 ton B)									
	Machine Operator (Diosna)									
	Feeder (Diosna)									
	Machine Operator 500									
	Feeder (500)									
	Feeder (500)									
	Cleaner - wash bay									
		32	9	13	22	10	3	5	8	27.50%
PACKING	Packing Supervisor									
	Assistant Supervisor									
	Machine Operator (GV4)									
	Machine Operator (GV4)									
	Packer 2 (GV4)									
	Packer 2 (GV4)									
	Machine Operator (Beta)									
	Machine Operator (Beta)									
	Packer 1 (Beta)									
	Packer 1 (Beta)									
	Machine Operator (Easyfill)									
	Packer 1 (Easyfill)									
	Packer 1 (Easyfill)									
	New Operator (Easyfill)									
	Packer 1 (Easyfill)									
	Packer 1 (Easyfill)									
	Ladies Packing									
	Packer 1 (Ladies)									
	Packer 1 (Ladies)									
	Packer 1 (Ladies)									
Packer 1 (Ladies)										
Machine Operator (NVL)										
Machine Operator (VBU)										
Feeder (Gantry)										
Assistant 1										
Assistant 2										
Assistant 3										
	72	24	23	47	25	9	8	17	58.75%	
WEIGHING	Scale/Oilroom Operator									
	Scale Operator 1									
	Scale Operator 2									
	Scale Operator 3									
	Scale Operator 4									
	Forklift Driver									
	16	5	6	11	5	2	2	4	13.75%	
Subtotal high exposure		120	38	42	80	40	14	15	29	
MEDIUM MILLING	Milling Supervisor									
	Milling Operator									
	Machine Operator									
	Feeder									
	Assistant									
		10	4	3	7	3	3	2	5	30.50%

PRODUCTION AREA

		PERSONEL DISTRIBUTION SPICE MILL				ENVIRONMENTAL SAMPLES				
		TOTAL	MORNING	AFTERNOON	TOTAL Morning and Afternoon	NIGHT	MORNING	AFTERNOON	TOTAL NUMBER OF SAMPLE	%
EXPOSURE WORK PROCESS JOBS	STOCK CONTROL	12	5	4	9	3	3	3	6	39.00%
	Shift supervisor									
	Ass supervisor									
	Reach Truck driver									
	Picker									
	TECHNICIANS	4	4		4		5		5	31%
	EM26	1	1		1					
	TENDERBITE PLANT	1	1		1					
	CLEANER	1	1		1					
	Subtotal medium exposure	29	16	7	23	6	11	5	16	
LOW										
ADMINISTRATION	8	8		8	0	5		5	30.00%	
LABORATORY	12	6	3	9	3	4	2	6	33%	
MCCP Admin										
Technician										
Assistants										
Student										
NAT DISTRIBUTION	15	5	5	10	5	3	3	6	37.00%	
Subtotal low exposure	35	19	8	27	8	12	5	17		
TOTAL	SPICE MILL	184			130				62	

NIOSH OESSM sampling method

Sample size for TOP 10% and CONFIDENCE 0.95 (Table A-2 was used)

Sample size 62

Appendix F

Respiratory Questionnaire

Occupational Allergy among Spice Workers

University of Cape Town

UNIVERSITY OF CAPE TOWN
OCCUPATIONAL ALLERGY AMONG SPICE MILL WORKERS
FREDDY HIRSCH GROUP - 2008
ENGLISH QUESTIONNAIRE

Card 1
 1-3

Survey Number

A. IDENTIFICATION DATA

1. Surname _____

2. First name/s _____

3. Address _____

4. Work number _____

4-10

5. Date of birth: Day _____ Month _____ Year _____

11-16

6. Gender: Male (1)
 Female (2)

17

7. Home Language: English (1)
 Afrikaans (2)
 Xhosa (3)
 Other (4)

18

8. Interviewer's initials _____

19

9. Date of interview: Day _____ Month _____ Year _____

20-25

10. Spice Mill Factory _____

26-27

11. Are you a casual or permanent worker?
 Casual (1)
 Permanent (2)

28

12.1 Date of last work shift?
 Day _____ Month _____ Year _____

29-34

12.2 Which shift did you work today?
 07:00 - 15:00 (1)
 15:00 - 23:00 (2)
 23:00 - 07:00 (3)
 Other: _____

35

B.HEALTH PROBLEMS

Wheeze and tightness in the chest

1. Have you ever had wheezing or whistling in your chest in the past?

- Yes (1)
- No (2)

36

If YES, go on to Question 1.1
If NO, skip to Question 2

1.1 If yes, when was the first time you had these symptoms.

Date: Month _____ Year _____

37-40

1.2 Have you had wheezing or whistling in your chest at any time in the **last 12 months?**

- Yes (1)
- No (2)

41

If YES, go on to Question 1.2.1
If NO, skip to Question 3

1.2.1 Have you been short of breath when the wheezing noise was present?

- Yes (1)
- No (2)

42

1.2.2 Have you had this wheezing or whistling when you did not have a cold or flu?

- Yes (1)
- No (2)

43

2. Have you been woken up with a feeling of tightness in your chest at any time in the **last 12 months?**

- Yes (1)
- No (2)

44

Shortness of breath

3. Have you had an attack of shortness of breath that came on during the daytime when you were at rest at any time in the **last 12 months?**

- Yes (1)
- No (2)

45

4. Have you had an attack of shortness of breath that came on following running or exercise at any time in the **last 12 months?**

Yes (1)
No (2)

46

5. Have you been woken by an attack of shortness of breath at any time in the **last 12 months?**

Yes (1)
No (2)

47

Cough and phlegm from the chest

6. Have you been woken by an attack of coughing at any time in the **last 12 months?**

Yes (1)
No (2)

48

7. Do you usually cough first thing in the morning?

Yes (1)
No (2)

49

8. Do you usually cough during the rest of the day, or at night?

Yes (1)
No (2)

50

If YES, go on to Question 8.1

If NO, skip to Question 9

8.1 Do you cough like this on most days/nights for as much as three or more months in each of the last two years?

Yes (1)
No (2)

51

9. Do you usually bring up any phlegm from your chest first thing in the morning?

Yes (1)
No (2)

52

10. Do you usually bring up any phlegm from your chest during the day, or at night?

Yes (1)
No (2)

53

If YES, go on to Question 10.1

If NO, skip to Question 11

10.1 Do you bring up phlegm like this on most days/
nights for as much as three or more months in each of
the last two years?

Yes (1)
No (2)

54

Breathing

11. Do you ever have trouble with your breathing?

Yes (1)
No (2)

55

If YES, go on to Question 11.1

If NO, skip to Question 12

11.1 Do you have this trouble:

Give all options at once
Insert a cross (X) next to one answer only

- a) continuously so that your breathing is never
quite right? _____
- b) repeatedly, but it goes away completely
between the times when it troubles you? _____
- c) only rarely? _____

56

12. Are you disabled from walking by a condition other
than heart or lung disease?

Yes (1)
No (2)

57

If YES, state the condition _____
and go on to Question 13
If NO, go to Question 12.1

12.1 Are you troubled by shortness of breath when
hurrying on level ground or walking up a slight hill?

Yes (1)
No (2)

58

If YES, go on to Question 12.1.1

If NO, skip to Question 13

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

- Yes (1)
No (2)

59

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

- Yes (1)
No (2)

60

Asthma

13. Have you ever had asthma?

- Yes (1)
No (2)

61

If YES, go on to Question 13.1

If NO, skip to Question 13.8

13.1 If yes, was this confirmed by a doctor?

- Yes (1)
No (2)

62

13.2 How old were you when you were told you have asthma?

63

Give all options at once

Insert a cross (X) next to one answer only

- a) Only before you were 17 years old _____
b) Only at the age of 17 years or older _____
c) Both _____

The following references to "attack" of asthma refers to episodes of wheezing, shortness of breath, chest tightness or cough attributed to asthma

13.3.1 How old were you when you had your first attack of asthma?

_____ years old

64-65

13.3.2 How old were you when you had your most recent attack of asthma?

_____ years old

66-67

13.4.1-6 Which months of the year do you usually have attacks of asthma?

13.4.1 January/February

Yes (1)
No (2)

68

13.4.2 March/April

Yes (1)
No (2)

69

13.4.3 May/June

Yes (1)
No (2)

70

13.4.4 July/August

Yes (1)
No (2)

71

13.4.5 September/October

Yes (1)
No (2)

72

13.4.6 November/December

Yes (1)
No (2)

73

13.5 Have you had an attack of asthma in the last 12 months?

Yes (1)
No (2)

Card 2

1

If YES, go on to Question 13.5.1

If NO, skip to Question 13.6

13.5.1 How often have you had an attack of asthma in the last 12 months?

2

Give all options at once

Insert a cross (X) next to one answer only

- a) Every day _____
- b) More than 2 times a week _____
- c) More than 1 time per month _____
- d) 3 to 12 times in the whole year _____
- e) 1 to 2 times in the whole year _____

13.6 Are your chest symptoms caused by, or made worse by any of the following:

Answer all questions

13.6.1 Contact with animals/pets

Yes (1)

 3

No (2)

13.6.2 Grass or flowers

Yes (1)

 4

No (2)

13.6.3 Heavy exercise

Yes (1)

 5

No (2)

13.6.4 Breathing cold air

Yes (1)

 6

No (2)

13.6.5 Dusts or sprays at work

Yes (1)

 7

No (2)

13.6.6 Tobacco smoke

Yes (1)

 8

No (2)

13.6.7 Change in the weather

Yes (1)

 9

No (2)

13.6.8 Spices/Spicy foods

Yes (1)

 10

No (2)

13.7 Do your chest symptoms seem better or worse when you are away from work (for example, on weekends, off-shift and vacations)?

 11

Give all options at once

Insert a cross (X) next to one answer only

a) Stay the same _____

b) Get better _____

c) Get worse _____

13.8 Does being at work ever make your chest tight or wheezy?

Yes (1)

 12

No (2)

If YES, go on to Question 13.8.1
If NO, skip to Question 13.9

13.8.1 When did you first notice having problems with chest tightness or wheeze at work?

Date: Month _____ Year _____

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	13-16
--------------------------	--------------------------	--------------------------	--------------------------	-------

13.8.2 Is there anything that you work with that causes you to have these chest symptoms?

Yes (1)
No (2)

<input type="checkbox"/>	17
--------------------------	----

If YES, go on to Question 13.8.3 (specify garlic, onion, ginger etc or any other substance)
If NO, skip to Question 13.9

13.8.3 What do you think is causing these symptoms?

<input type="checkbox"/>	18-19
<input type="checkbox"/>	20-21
<input type="checkbox"/>	22-23
<input type="checkbox"/>	24-25

13.9 Have you ever had to change or leave your work area, either temporarily or permanently, in this spice mill or any other spice mill because of any chest symptoms?

Yes (1)
No (2)

<input type="checkbox"/>	26
--------------------------	----

If YES, go on to Question 13.9.1
If NO, skip to Question 13.10

13.9.1 What type of job were you doing when this happened?

<input type="checkbox"/>	<input type="checkbox"/>	27-28
--------------------------	--------------------------	-------

13.9.2 Was this a job in this spice mill?

Yes (1)
No (2)

<input type="checkbox"/>	29
--------------------------	----

If YES, go on to Question 13.9.2.1
If NO, skip to Question 13.10

13.9.2.1 What area/section did you move to?

<input type="checkbox"/>	<input type="checkbox"/>	30-31
--------------------------	--------------------------	-------

13.9.2.2 What job did you do there?

<input type="checkbox"/>	<input type="checkbox"/>	32-33
--------------------------	--------------------------	-------

13.9.2.3 Did your symptoms improve when you changed jobs?

Yes (1)
No (2)

34

13.10 Have you ever worked in a job or jobs that exposed you to vapours, gas, dust (including flour, spice/ grain) or fumes?

Yes (1)
No (2)

35

If YES, go on to Question 13.10.1.
List the jobs beginning with the most recent
If NO, skip to Question 13.11

13.10.1 What was or is this job? _____
(if current job write 'current job' & specify)

36-37

13.10.2 Before that? _____

38-39

13.10.3 Before that? _____

40-41

13.11 Has there ever been an instance when you inhaled a large amount of vapour, gas, dust or fumes in any of these jobs that resulted in you developing a tight chest, wheeze or cough?

Yes (1)
No (2)

42

If YES, go on to Question 13.11.1.
If NO, skip to Question 13.12

13.11.1 What was or is this job? _____
(if current job write 'current job' & specify)

43-44

13.12 Are you using any medicines, including inhalers/ pumps, nebulizers, syrups or tablets, for asthma or breathing problems?

Yes (1)
No (2)

45

If YES, go on to Question 13.12.1, showing examples of each
If NO, skip to question 13.13

13.12.1 Which medicines?

46
 47
 48

13.12.2 Do you take these medicines every day even when you do not have any trouble breathing?

- Yes (1)
- No (2)

49

13.13 Have you ever been treated for any of the following:

Answer all questions

13.13.1 Repeated chest infections as a child

- Yes (1)
- No (2)
- UNK (3)

50

13.13.2 Tuberculosis (TB)

- Yes (1)
- No (2)
- UNK (3)

51

13.13.3 Chronic bronchitis

- Yes (1)
- No (2)
- UNK (3)

52

Nose and eye symptoms

14. Have you ever had any nose or eye problems or allergies such as hay fever?

- Yes (1)
- No (2)

53

14.1 How old were you when you first noticed these symptoms?

_____ years old

54-55

If YES, go on to Question 14.2 Answer all questions

If NO, skip to Question 14.4

14.2 During the past 12 months have you had two or more episodes of:

14.2.1 sneezy, itchy or runny nose when you did not have a cold or flu?

- Yes (1)
- No (2)

56

14.2.2 red, itchy or watery eyes

- Yes (1)
- No (2)

57

14.2.3 Do you usually have the nose or eye symptoms at any particular time of the year?

- Yes (1)
- No (2)

58

14.2.3.1 If YES, which is the worst season?

59

Give all options at once
Insert a cross (X) next to one answer only

- a) Winter _____
- b) Spring _____
- c) Summer _____
- d) Autumn _____

If YES to any of the above in question 14.2, go on to Question 14.3
If NO, skip to Question 14.4

14.3 Do your nose or eye symptoms seem better or worse when you are away from work (for example, on weekends, off-shift and vacations)?

60

Give all options at once
Insert a cross (X) next to one answer only

- a) Stay the same _____
- b) Get better _____
- c) Get worse _____

14.4 Does being at work ever cause you to have sneezy/ itchy/runny nose or red/itchy/watery eyes?

- Yes (1)
- No (2)

61

If YES to any one of the above, go on to Question 14.4.1
If NO, skip to Question 14.6

14.4.1 Since when have you been having these symptoms at work?

Date: Month ____ Year ____

62-65

14.4.2 Is there anything that you work with that causes you to have these symptoms?

- Yes (1)
- No (2)

66

If YES, go on to Question 14.4.3 (specify garlic, onion, ginger etc or any other substance)

If NO, skip to Question 14.5

14.4.3 What do you think is causing these symptoms?

<input type="checkbox"/>	<input type="checkbox"/>	67-68
<input type="checkbox"/>	<input type="checkbox"/>	69-70
<input type="checkbox"/>	<input type="checkbox"/>	71-72
<input type="checkbox"/>	<input type="checkbox"/>	73-74

14.5 Are you using any medicines, including nose sprays, drops, tablets or injections, for your nose or eye symptoms at present?

- Yes (1)
- No (2)

75

If YES, go on to Question 14.5.1
 If NO, go on to Question 14.6

Present a chart with different samples of allergy medicines (N.B. a worker might show you his/her medicines).

14.5.1 Which medicines?

76

77

14.6 Did you have hay fever (itchy or watery eyes/nose) as a child?

- Yes (1)
- No (2)

78

Skin symptoms

15. Have you ever had any kind of skin problem either at home or at work?

- Yes (1)
- No (2)

Card 3

1

If YES, go on to Question 15.1
 If NO, skip to Question 15.4.4

15.1 How old were you when you **first** noticed this skin problem?

_____ years old

2-3

15.2 During the past **12 months** have you had any skin problems that occurred **2 or more times**?

- Yes (1)
- No (2)

4

If Yes, which of the following problems did you have?

Go through each option in the table below and circle the appropriate response.

	Forearms	Whole
	Hands	Body
15.2.1		
itchy or	Yes/No	Yes/No
scratchy skin		
15.2.2		
hives	Yes/No	Yes/No
("bommels")		

5
 6

7
 8

15.2.3	Forearms	Whole
	Hands	Body
dry, scaly skin	Yes/No	Yes/No
15.2.4		
redness of the skin	Yes/No	Yes/No
15.2.5		
blisters or weeping skin	Yes/No	Yes/No
15.2.6		
burning skin	Yes/No	Yes/No
15.2.7		
rash within an hour of contact with a spice product or food item	Yes/No	Yes/No
15.2.8		
Other?	Yes/No	Yes/No
Specify:		

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 13
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 15
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 17
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 19
 20

If YES, to any of the above go on to Question 15.3
 If NO, skip to Question 15.4

15.3 Do your skin problems seem better or worse when you are away from work (for example, on weekends, off-shift and vacations)?

 21

Give all options at once
 Insert a cross (X) next to one answer only

- a) Stay the same _____
- b) Get better _____
- c) Get worse _____

15.4 Does being at work ever cause you to have skin problems?

 22

Yes (1)
 No (2)

If YES, go on to Question 15.4.1
 If NO, skip to Question 15.4.4

15.4.1 Since when have you been having these skin problems at work?

Date: Month ____ Year ____

 23-26

15.4.2 Is there anything that you work with that makes these skin problems worse?

Yes (1)
 No (2)

 27

If YES, go on to Question 15.4.3 (specify garlic, onion, ginger etc) or any other substance

If NO, skip to Question 15.4.4

15.4.3 What do you think is causing these skin problems?

<input type="checkbox"/>	28-29
<input type="checkbox"/>	30-31
<input type="checkbox"/>	32-33

15.4.4 Have you ever bruised or injured your fingers or hands while working in the spice mill?

- Yes (1)
No (2)

34

15.5 How many times do you wash your hands in the course of a day?

35

Give all options at once

Insert a cross (X) next to one answer only

- 0 _____
1 time _____
2-3 times _____
4-5 times _____
6 or more _____

15.6 Are you using any medicines, including any creams or ointments, for your skin problems at present?

- Yes (1)
No (2)

36

If YES, go on to Question 15.6.1

If NO, skip to next question 15.7

15.6.1 Which medicines?

<input type="checkbox"/>	37
<input type="checkbox"/>	38
<input type="checkbox"/>	39

15.7 Did you have eczema as a child?

- Yes (1)
No (2)

40

Other allergic conditions

16. Are you allergic to insect stings or bites?

- Yes (1)
No (2)

41

If YES, go on to Question 16.1

If NO, skip to Question 17

16.1.1-3 What kind of reactions do you have?

16.1.1 Breathing difficulty, feeling faint, fever?

- Yes (1)
No (2)

42

16.1.2 Redness, itching or swelling at the sting site

Yes (1)
No (2)

43

16.1.3 Other: _____

44

17. Have you ever had any difficulty with your breathing after taking medications or injections that you did not have before?

Yes (1)
No (2)

45

If YES, go on to Question 17.1

If NO, skip to 18.1

17.1 Which medicines?

46

18.1-6 When you are near animals (such as cats, dogs or horses), near feathers (including pillows, quilts or duvets), near grass and flowers, or in a dusty part of the house, do you **ever**

18.1 Start to cough?

Yes (1)
No (2)

47

18.2 Start to wheeze?

Yes (1)
No (2)

48

18.3 Get a tight chest?

Yes (1)
No (2)

49

18.4 Start to feel short of breath?

Yes (1)
No (2)

50

18.5 Get a runny/stuffy nose or sneeze?

Yes (1)
No (2)

51

18.6 Get itchy or watery eyes?

Yes (1)
No (2)

52

18.7 Get itchy skin/rash?

Yes (1)
No (2)

53

19. Have you ever had an illness or trouble caused by eating a particular type of food/spice?

Yes (1)
No (2)

54

If YES, go on to Question 19.1
If NO, skip to section C

19.1 What type of food/fruit/spice was this?

55

19.1.1-6 Did this illness or trouble include:

19.1.1 Itchy skin or rash

Yes (1)
No (2)

56

19.1.2 Diarrhoea or vomiting

Yes (1)
No (2)

57

19.1.3 Runny or stuffy nose

Yes (1)
No (2)

58

19.1.4 Severe headaches

Yes (1)
No (2)

59

19.1.5 Breathlessness/tight chest/wheeze

Yes (1)
No (2)

60

19.1.6 Other: _____

61

19.2 Was the food canned or preserved?

Yes (1)
No (2)

62

19.3 Do you experience these problems when you drink fizzy drinks also?

Yes (1)
No (2)

63

C. FAMILY HISTORY

1. Do/did any members of your family (blood relatives) ever have any kind of allergies?

64

Do not include relatives by marriage

If family history is completely unknown (subject is adopted, etc.), mark UNK and do not complete table. Move to next section

Yes (1)
No (2)
UNK (3)

If YES, complete table below. Insert a cross (X) in the appropriate block for each option

Type of Allergy	NO ONE in family	YES, present in the family			Do Not Know
		Parent	Brother/Sister	Child	
1.1 Hay fever	1	2	3	4	5
1.2 Eczema	1	2	3	4	5
1.3 Asthma	1	2	3	4	5
1.4 Spice-related allergy	1	2	3	4	5
1.5 Flour-related allergy	1	2	3	4	5
1.6 Other allergy	1	2	3	4	5
Specify:					

 65

 66

 67

 68

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 71

D. SMOKING HISTORY

Card 4

1. Have you ever smoked tobacco (cigarettes or pipe) for as long as a year?

'YES' means at least 20 packs of cigarettes or 360 grams of tobacco in a lifetime or at least one cigarette per day for one year

Yes (1)
No (2)

 1

If YES, go on to Question 1.1
If NO, skip to Question 2

1.1 How old were you when you started smoking?

_____ years old

 2-3

1.2 Do you now smoke?

'YES' means smoking tobacco in the last month or more

Yes (1)
No (2)

 4

If YES, go on to Question 1.2.1
If NO, skip to Question 1.3.1

1.2.1-2. How much do you now smoke on average?

1.2.1 Number of cigarettes per day _____

 5-6

1.2.2 Pipe tobacco in grams/week _____

 7-9

1.3. Have you stopped smoking completely?

Yes (1)
No (2)

 10

If YES, go on to Question 1.3.1
 If NO, skip to Question 1.4

1.3.1. How old were you when you stopped smoking completely?

_____ years old

11-12

1.3.1.1 How many years in total did you smoke cigarettes? (Do not include the years you stopped before you started again)

_____ years

13-14

1.3.2.1-2 On average of the entire time you smoked, how much did you smoke?

1.3.2.1 Number of cigarettes per day _____

15-16

1.3.2.2 Pipe tobacco in grams/week _____

17-19

1.4 Do you or did you inhale the smoke?

Yes (1)

No (2)

20

2. Have you been regularly exposed to tobacco smoke from other people smoking cigarettes or pipe in the last 12 months?

'Regularly' means on most days or nights

Yes (1)

No (2)

21

E. DIETARY HISTORY/DOMESTIC ACTIVITIES

1. How often do you eat the following spice products or spicy food blends in the last 12 months?

Go through each spice product option and circle number in the block for each option

Type of spice product	Daily	1 to 3 times a week	1 to 3 times per month	Never
1.1 Nutmeg	1	2	3	4
1.2 Bayleaf	1	2	3	4
1.3 Cinnamon	1	2	3	4
1.4 Blackpepper	1	2	3	4
1.5 Allspice/pimento	1	2	3	4
1.6 Celery	1	2	3	4
1.7 Fennel	1	2	3	4
1.8 Parseley	1	2	3	4
1.9 Mustard	1	2	3	4
2.0 Chilli Pepper	1	2	3	4
2.1 Paprika	1	2	3	4
2.2 Thyme	1	2	3	4
2.3 Marjoram	1	2	3	4
2.4 Garlic powder	1	2	3	4
2.5 Onion powder	1	2	3	4
2.6 Ginger	1	2	3	4
3.0 Wheat	1	2	3	4
3.1 Maize	1	2	3	4
4.0 Tomato	1	2	3	4
5.0 Egg	1	2	3	4

Card 4

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2. Have you changed your diet or avoided certain spice (eg. garlic, onion, ginger etc/other wheat/maize) products because they do not agree with you when you eat them?

- Yes (1)
- No (2)

 42

If YES, go on to Question 2.1

If NO, skip to next Section F on HSE & Training

2.1 What spice/flour products have you avoided?

 43
 44

3. Do you use spices at home?

- Yes (1)
- No (2)

 45

If YES, go on to Question 3.2

If NO, go to Question 3.1

3.1 If no, does any one else prepare spicy food at home?

- Yes (1)
- No (2)

 46

3.2 How often do you do prepare spicy food at home?

- a) once a month _____
- b) 2-3 times a month _____
- c) 2-3 times per week _____
- d) once a week _____
- e) everyday _____

 47

3.3 What spice blends do you use ?

- a) Spicy barbecue seasoning _____
- b) Cayne Pepper _____
- c) Mixed spice _____
- d) Peri-Peri _____
- f) Other: _____

 48 49 50 51

Specify: _____

 52

3.4 How often do you use the spice blends?

- a) once a month _____
- b) 2-3 times a month _____
- c) 2-3 times per week _____
- d) once a week _____
- e) everyday _____

 53

F. HEALTH AND SAFETY EDUCATION AND TRAINING

1. What are the health problems caused by spice dust?

 54-55
 56-57
 58-59

2. Have you had any health and safety training on how to protect yourself when working with spice dust?

- Yes (1)
- No (2)

 60

G. WORK HISTORY IN THE SPICE INDUSTRY

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

_____ years
 _____ months

61-64

Present job

2. How long have you been working in your current job?

_____ years
 _____ months

65-68

3. In which area/section are you currently working?

69-70

3.1 What is your job in this area/section?

Job Title _____

71-72

get a short description of the job

3.2 Which of the following spice blends or food products do you mill/work with on a regular basis (1/more times a week)?

Spice Blends	Yes	No	UNK
3.2a1 Straight pack garlic	(1)	(2)	(3)
3.3a2 Straight pack onion	(1)	(2)	(3)
3.3a3 Straight pack chilli pepper	(1)	(2)	(3)
3.3b Brines country bird IQF	(1)	(2)	(3)
3.3c Seasonings barbeque	(1)	(2)	(3)
3.3d Sprinkles barbeque	(1)	(2)	(3)
3.3e Marinades barbeque	(1)	(2)	(3)
3.3f1 Sodium benzoate	(1)	(2)	(3)
3.3f2 Sodium sulphites	(1)	(2)	(3)
3.3f3 Nitrites	(1)	(2)	(3)
3.3g Other:	(1)	(2)	(3)
Specify: _____			

Card 5

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3.3 Which of the following ingredients do you work with on a regular basis (1/more times a week)?

Spices and food product	Yes	No	UNK
3.3a1	Nutmeg	(1)	(2) (3)
3.3a2	Bayleaf	(1)	(2) (3)
3.3a3	Cinnamon	(1)	(2) (3)
3.3a4	Black pepper	(1)	(2) (3)
3.3b1	Allspice/Pimento	(1)	(2) (3)
3.3b2	Celery	(1)	(2) (3)
3.3b3	Fennel	(1)	(2) (3)
3.3b4	Parseley	(1)	(2) (3)
3.3c	Mustard white	(1)	(2) (3)
3.3d1	Chilli pepper	(1)	(2) (3)
3.3d2	Paprika	(1)	(2) (3)
3.3d3	Thyme	(1)	(2) (3)
3.3d4	Marjoram	(1)	(2) (3)
3.3f1	Garlic powder	(1)	(2) (3)
3.3f2	Onion powder	(1)	(2) (3)
3.3g	Ginger	(1)	(2) (3)
3.3h1	Wheat/flour	(1)	(2) (3)
3.3h2	Maize/starch	(1)	(2) (3)
3.3i	Sodium carbonate	(1)	(2) (3)
3.3j	Papain 6100 liquid	(1)	(2) (3)
3.3k	Curry	(1)	(2) (3)
3.3l	Tomato	(1)	(2) (3)

Other:

Specify: _____

Specify: _____

3.4 Do you ever do other jobs during your shift on a regular basis (almost every day)?

Yes **No**
(1) (2)

If **Yes**, which jobs? _____

3.5 How much spice dust would you say your current job produces:

Give all options at once

Insert a cross (X) next to one answer only

- a) None _____
- b) A little _____
- c) An average amount _____
- d) A lot _____

Card 5

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40-41

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43

3.5.1 What aspect of your work would you say is very dusty?

- | | | | | |
|---|-------------------|------------------|-------------------|-----------------------------|
| a) Milling spices | Yes
(1) | No
(2) | N/A
(3) | <input type="checkbox"/> 44 |
| b) Weighing spices | Yes
(1) | No
(2) | N/A
(3) | <input type="checkbox"/> 45 |
| c) Blending/adding spices into hoppers | Yes
(1) | No
(2) | N/A
(3) | <input type="checkbox"/> 46 |
| d) Packing spices | Yes
(1) | No
(2) | N/A
(3) | <input type="checkbox"/> 47 |
| e) Scooping spices | Yes
(1) | No
(2) | N/A
(3) | <input type="checkbox"/> 48 |
| f) Handling additives sodium sulphites/ sodium benzoate/ nitrites | Yes
(1) | No
(2) | N/A
(3) | <input type="checkbox"/> 49 |
| g) other | Yes
(1) | No
(2) | N/A
(3) | <input type="checkbox"/> 50 |

Specify: _____ 51

3.5.1.1 What type of cleaning activities in your daily work are very dusty.

3.5.1.1.1 Cleaning work table surfaces?

- | | | |
|-------------------|------------------|-----------------------------|
| Yes
(1) | No
(2) | <input type="checkbox"/> 52 |
|-------------------|------------------|-----------------------------|

3.5.1.1.2 Sweeping floors?

- | | | |
|-------------------|------------------|-----------------------------|
| Yes
(1) | No
(2) | <input type="checkbox"/> 53 |
|-------------------|------------------|-----------------------------|

3.5.1.1.3 Cleaning equipment (hoppers, blenders)

- | | | |
|-------------------|------------------|-----------------------------|
| Yes
(1) | No
(2) | <input type="checkbox"/> 54 |
|-------------------|------------------|-----------------------------|

3.5.1.1.4 Wet mopping floors

- | | | |
|-------------------|------------------|-----------------------------|
| Yes
(1) | No
(2) | <input type="checkbox"/> 55 |
|-------------------|------------------|-----------------------------|

3.5.2 How far do you work from the source of the dust? 56

Give all options at once

Insert a cross (X) next to one answer only

- | | |
|-----------------------------|-------|
| a) Right next to the source | _____ |
| b) About 1-2 metres away | _____ |
| c) More than 3 metres away | _____ |
| d) Does not apply | _____ |

3.6 Do you use any personal protective equipment on a regular basis (almost every day) while doing your job?

- | | | |
|-------------------|------------------|-----------------------------|
| Yes
(1) | No
(2) | <input type="checkbox"/> 57 |
|-------------------|------------------|-----------------------------|

4.1.3 Permanent/casual: _____

5

4.1.4. How long did you work in this job?

_____ years
 _____ months

6-9

4.1.5 Which of the following spice blends or food products did you mill/work with on a regular basis (1/more times a week)?

Spice Blends	Yes	No	UNK
4.1.5a1 Straight pack garlic	(1)	(2)	(3)
4.1.5a2 Straight pack onion	(1)	(2)	(3)
4.1.5a3 Straight pack chilli pepper	(1)	(2)	(3)
4.1.5b Brines country bird IQF	(1)	(2)	(3)
4.1.5c Seasonings barbeque	(1)	(2)	(3)
4.1.5d Sprinkles barbeque	(1)	(2)	(3)
4.1.5e Marinades barbeque	(1)	(2)	(3)
4.1.5f1 Sodium benzoate	(1)	(2)	(3)
4.1.5f2 Sodium sulphites	(1)	(2)	(3)
4.1.5f3 Nitrites	(1)	(2)	(3)
4.1.5g Other:	(1)	(2)	(3)
Specify: _____			

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4.1.6 Which of the following ingredients did you work with on a regular basis (1/more times a week)?

Spices and food product	Yes	No	UNK
4.1.6a1 Nutmeg	(1)	(2)	(3)
4.1.6a2 Bayleaf	(1)	(2)	(3)
4.1.6a3 Cinnamon	(1)	(2)	(3)
4.1.6a4 Black pepper	(1)	(2)	(3)
4.1.6b1 Allspice/Pimento	(1)	(2)	(3)
4.1.6b2 Celery	(1)	(2)	(3)
4.1.6b3 Fennel	(1)	(2)	(3)
4.1.6b4 Parsley	(1)	(2)	(3)
4.1.6c Mustard white	(1)	(2)	(3)
4.1.6d1 Chilli pepper	(1)	(2)	(3)
4.1.6d2 Paprika	(1)	(2)	(3)
4.1.6d3 Thyme	(1)	(2)	(3)
4.1.6d4 Marjoram	(1)	(2)	(3)
4.1.6f1 Garlic powder	(1)	(2)	(3)
4.1.6f2 Onion powder	(1)	(2)	(3)
4.1.6g Ginger	(1)	(2)	(3)
4.1.6h1 Wheat/flour	(1)	(2)	(3)
4.1.6h2 Maize/starch	(1)	(2)	(3)
4.1.6i Sodium carbonate	(1)	(2)	(3)
4.1.6j Papain 6100 liquid	(1)	(2)	(3)
4.1.6k Curry	(1)	(2)	(3)
4.1.6l Tomato	(1)	(2)	(3)

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Other:

Specify: _____

Specify: _____

44
 45

4.1.7 How much spice dust would you say that this job produced:

46

Give all options at once
Insert a cross (X) next to one answer only

- a) None _____
- b) A little _____
- c) An average amount _____
- d) A lot _____

4.1.8 What aspect of your work would you say was very dusty?

a) Milling spices **Yes** **No** **N/A**
 (1) (2) (3)

47

b) Weighing spices **Yes** **No** **N/A**
 (1) (2) (3)

48

c) Blending/adding spices into hoppers **Yes** **No** **N/A**
 (1) (2) (3)

49

d) Packing spices **Yes** **No** **N/A**
 (1) (2) (3)

50

e) Scooping spices **Yes** **No** **N/A**
 (1) (2) (3)

51

f) Handling additives sodium sulphites/
sodium benzoate/
nitrites **Yes** **No** **N/A**
 (1) (2) (3)

52

g) other **Yes** **No** **N/A**
 (1) (2) (3)

53

Specify: _____

54

4.1.8.1. What type of cleaning activities in your daily work were very dusty.

4.1.8.1.1. Cleaning work table surfaces?

Yes **No**
(1) (2)

55

4.1.8.1.2 Sweeping floors?

Yes **No**
(1) (2)

56

4.1.8.1.3 Cleaning equipment (hoppers, blenders)

Yes **No**
(1) (2)

57

4.1.8.1.4 Wet mopping floors

Yes **No**
(1) (2)

58

4.1.9 How far did you work from the source of the dust?

59

4.2.4. How long did you work in this job?

_____ years
 _____ months

				6-9
--	--	--	--	-----

4.2.5 Which of the following spice blends or food products did you mill/work with on a regular basis (1/more times a week)?

Spice Blends	Yes	No	UNK
4.2.5a1 Straight pack garlic	(1)	(2)	(3)
4.2.5a2 Straight pack onion	(1)	(2)	(3)
4.2.5a3 Straight pack chilli pepper	(1)	(2)	(3)
4.2.5b Brines country bird IQF	(1)	(2)	(3)
4.2.5c Seasonings barbeque	(1)	(2)	(3)
4.2.5d Sprinkles barbeque	(1)	(2)	(3)
4.2.5e Marinades barbeque	(1)	(2)	(3)
4.2.5f1 Sodium benzoate	(1)	(2)	(3)
4.2.5f2 Sodium sulphites	(1)	(2)	(3)
4.2.5f3 Nitrites	(1)	(2)	(3)
4.2.5g Other:	(1)	(2)	(3)
Specify: _____			

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	21

4.2.6 Which of the following ingredients did you work with on a regular basis (1/more times a week)?

Spices and food product	Yes	No	UNK
4.2.6a1 Nutmeg	(1)	(2)	(3)
4.2.6a2 Bayleaf	(1)	(2)	(3)
4.2.6a3 Cinnamon	(1)	(2)	(3)
4.2.6a4 Black pepper	(1)	(2)	(3)
4.2.6b1 Allspice/Pimento	(1)	(2)	(3)
4.2.6b2 Celery	(1)	(2)	(3)
4.2.6b3 Fennel	(1)	(2)	(3)
4.2.6b4 Parsley	(1)	(2)	(3)
4.2.6c Mustard white	(1)	(2)	(3)
4.2.6d1 Chilli pepper	(1)	(2)	(3)
4.2.6d2 Paprika	(1)	(2)	(3)
4.2.6d3 Thyme	(1)	(2)	(3)
4.2.6d4 Marjoram	(1)	(2)	(3)
4.2.6f1 Garlic powder	(1)	(2)	(3)
4.2.6f2 Onion powder	(1)	(2)	(3)
4.2.6g Ginger	(1)	(2)	(3)
4.2.6h1 Wheat/flour	(1)	(2)	(3)
4.2.6h2 Maize/starch	(1)	(2)	(3)
4.2.6i Sodium carbonate	(1)	(2)	(3)
4.2.6j Papain 6100 liquid	(1)	(2)	(3)
4.2.6k Curry	(1)	(2)	(3)
4.2.6l Tomato	(1)	(2)	(3)

Other:

Specify: _____

Specify: _____

	22
	23
	24
	25
	26
	27
	28
	29
	30
	31
	32
	33
	34
	35
	36
	37
	38
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	40
	41
	42
	43

	44
	45

4.2.7 How much spice dust would you say that this job produced:

46

Give all options at once

Insert a cross (X) next to one answer only

- a) None _____
- b) A little _____
- c) An average amount _____
- d) A lot _____

4.2.8 What aspect of your work would you say was very dusty?

a) Milling spices **Yes** **No** **N/A**
(1) (2) (3)

47

b) Weighing spices **Yes** **No** **N/A**
(1) (2) (3)

48

c) Blending/adding spices into hoppers **Yes** **No** **N/A**
(1) (2) (3)

49

d) Packing spices **Yes** **No** **N/A**
(1) (2) (3)

50

e) Scooping spices **Yes** **No** **N/A**
(1) (2) (3)

51

f) Handling additives sodium sulphites/
sodium benzoate/
nitrites **Yes** **No** **N/A**
(1) (2) (3)

52

g) other **Yes** **No** **N/A**
(1) (2) (3)

53

Specify: _____

54

4.2.8.1. What type of cleaning activities in your daily work were very dusty.

4.2.8.1.1. Cleaning work table surfaces?

Yes **No**
(1) (2)

55

4.2.8.1.2 Sweeping floors?

Yes **No**
(1) (2)

56

4.2.8.1.3 Cleaning equipment (hoppers, blenders)

Yes **No**
(1) (2)

57

4.2.8.1.4 Wet mopping floors

Yes **No**
(1) (2)

58

4.2.9 How far did you work from the source of the dust?

59

Give all options at once
 Insert a cross (X) next to one answer only

- a) Right next to the source _____
- b) About 1-2 metres away _____
- c) More than 3 metres away _____
- d) Does not apply _____

4.2.10 Did you use any personal protective equipment on a regular basis (almost every day) while doing your job?

Yes No
 (1) (2)

60

If NO, skip to Question 4.3.1 or 5 if no other jobs
 If YES, continue with Question 4.2.10.1

4.2.10.1 Which of the following personal protective equipment did you use on a regular basis (almost every day)?

4.2.10.1.1 Goggles:

Yes No
 (1) (2)

61

4.2.10.2 Gloves:

Yes No
 (1) (2)

62

4.2.10.3 Mask: FFP1

Yes No
 (1) (2)

63

4.2.10.4 Coveralls:

Yes No
 (1) (2)

64

4.2.10.5 Other: _____

65

If NO to all of the previous questions, skip to Question 4.3.1 or 5
 If YES to any one of the above questions, continue with Question 4.2.11.1

4.2.11.1 Goggles _____ years

66-68

4.2.11.2 Gloves: _____ years

69-71

4.2.11.3 Mask: FFP1 _____ years

72-74

4.2.11.4 Coveralls: _____ years

75-77

4.2.11.5 Other: _____ years

78-80

Job 3

4.3.1 Area/section _____

Card 8
 1-2

4.3.2 Job Title _____

3-4

get a short description of the job

4.3.3 Permanent/casual: _____

5

4.3.7 How much spice dust would you say that this job produced:

46

Give all options at once

Insert a cross (X) next to one answer only

- a) None _____
- b) A little _____
- c) An average amount _____
- d) A lot _____

4.3.8 What aspect of your work would you say was very dusty?

a) Milling spices **Yes** **No** **N/A**
(1) (2) (3)

47

b) Weighing spices **Yes** **No** **N/A**
(1) (2) (3)

48

c) Blending/adding spices into hoppers **Yes** **No** **N/A**
(1) (2) (3)

49

d) Packing spices **Yes** **No** **N/A**
(1) (2) (3)

50

e) Scooping spices **Yes** **No** **N/A**
(1) (2) (3)

51

f) Handling additives sodium sulphites/ sodium benzoate/ nitrites **Yes** **No** **N/A**
(1) (2) (3)

52

g) other **Yes** **No** **N/A**
(1) (2) (3)

53

Specify: _____

54

4.3.8.1. What type of cleaning activities in your daily work were very dusty.

4.3.8.1.1. Cleaning work table surfaces?

Yes **No**
(1) (2)

55

4.3.8.1.2 Sweeping floors?

Yes **No**
(1) (2)

56

4.3.8.1.3 Cleaning equipment (hoppers, blenders)

Yes **No**
(1) (2)

57

4.2.8.1.4 Wet mopping floors

Yes **No**
(1) (2)

58

Previous work in other spice mills/factories

5. Have you worked in any other spice mills in the past two years?

Yes (1)
No (2)

Card 9 1

If NO, skip to question 6
If YES, continue with question 5.1

5.1 Why did you change jobs?

2

5.2 What is the total amount of time you have worked in the spice mill industry before you started working in this spice mill?

Years _____ Months _____

3-6

Previous work experience

6. Name all the previous workplaces that you have worked in, when not working in this spice mill/factory or before coming to work in this spice mill:

Start with the most recent job and work backwards (including all other spice mills and jobs done)

Name of Company	What did you do?	Job Title (what did you do?)	Date start (Year)	Date stop (Year)	Total (yrs)

7-8
 9-10

THANK YOU FOR ANSWERING THE QUESTIONNAIRE

Appendix G

Lung function pre-test questionnaire

Spice Mill Study

University of Cape Town

**UNIVERSITY OF CAPE TOWN
OCCUPATIONAL ALLERGY AMONG SPICE MILL WORKERS
FREDDY HIRSCH GROUP – 2008**

LFT PRE-TEST DATA COLLECTION SHEET

Survey Number										Card 1
Work number										1-3
Date										4-10
										11-16
	DAY	MONTH	YEAR							

1. Have you had a heart attack or stroke in the last 3 months? 1. YES 2. NO 17
2. Do you have epilepsy? 1. YES 2. NO 18
3. Have you had any recent operation (in the last 12 months)? 1. YES 2. NO 19
 If **Yes**, what type and how many months ago?
 _____ (months)

If **YES**, to any of the above, indicate to the person that the lung function tests will not be done. If **NO**, proceed with the rest of the screening questions

4. For Women:

- 4.1 Are you Pregnant? 1. YES 2. NO 20
- 4.2 Are you Breastfeeding? 1. YES 2. NO 21

If **Pregnant**, indicate to the person that the Lung Function Test will not be done today.
 If **Breastfeeding**, proceed with Lung Function Test with Post-Bronchodilator. Proceed with the rest of the screening questions.

5. Have you had the flu or lung infection in the past 3 weeks? 1. YES 2. NO 22
 If **Yes**, how many days ago did it end? _____ days 23-24
6. Are you being treated for Tuberculosis? 1. YES 2. NO 25
 If **Yes**, for how long? _____ months _____ weeks 26-29

If YES, to either question No. 5 or 6, indicate to the person that the lung function tests will not be done today. Reschedule another appointment three weeks after the end of their illness or since the start of TB medication. If NO, continue with the rest of the questions.

7. Did you drink coffee, tea or coca-cola in the last one hour?

1. YES 2. NO ₃₀

8. Have you smoked in the last two hours?

1. YES 2. NO ₃₁

If YES to No. 8, reschedule the Lung Function Test test for later the same day (at least one hour since last cigarette) or another date. Other screening procedures can be done first.

9. Have you had asthma in the past?

1. YES 2. NO ₃₂

9.1 Do you have asthma now?

1. YES 2. NO ₃₃

10. Are you taking any medicine/s from a doctor or clinic at the moment for your lungs, any heart condition, or your eyes?

1. YES 2. NO ₃₄

10.1 If Yes, what are you taking and when did you last take them?

Names

No. of hours
since last dose

_____	_____
_____	_____
_____	_____

₃₅₋₃₆

₃₇₋₃₈

₃₉₋₄₀

If short-acting beta-2-agonist or anti-cholinergic inhalers used in the last 4 hours or long-acting MDI or theophylline used in last 8 hours, reschedule and counsel accordingly.

11. Have you had any of the following symptoms in the past 12 months? 1. YES 2. NO ₄₁

(at night, with exercise, exposure to cold air, viral infections, work exposures) **If yes, which ones?**

11.1 chest tightness 1. YES 2. NO ₄₂

11.2 shortness of breath 1. YES 2. NO ₄₃

11.3 wheezing or whistling in your chest 1. YES 2. NO ₄₄

11.4 dry cough 1. YES 2. NO ₄₅

12. Do you currently have any of these symptoms?

1. YES 2. NO

₄₆

If Yes, which ones?

12.1 chest tightness

1. YES 2. NO

₄₇

12.2 shortness of breath

1. YES 2. NO

₄₈

12.3 wheezing or whistling in your chest

1. YES 2. NO

₄₉

12.4 dry cough

1. YES 2. NO

₅₀

University of Cape Town

Appendix H

Lung function test data collection sheet

Spice Mill Study

University of Cape Town

**UNIVERSITY OF CAPE TOWN
OCCUPATIONAL ALLERGY AMONG SPICE MILL WORKERS
FREDDY HIRSCH GROUP – 2008**

LUNG FUNCTION TEST DATA COLLECTION SHEET

Survey Number

DAY				MONTH		YEAR	

Card 1
1-3
4-10
11-16

Work number

Date

1. Subject's blood pressure

--	--	--

systolic

[DO NOT PROCEED WITH LFT IF BP >180/110]

--	--	--

diastolic

2. Subject's DOB

Date

DAY				MONTH		YEAR	

17-22

3. Subject's age

YEARS

--	--

23-24

4. Subject's gender

MALE FEMALE

--	--

25

5.1 Subject's height

CENTIMETRES

--	--	--

26-28

5.2 Subject's weight

KILOGRAMS

--	--

29-30

6. When did you last work in the spice mill?

Date

--	--	--	--	--	--

31-36

BASELINE SPIROMETRY

7. PREDICTED FEV₁

--	--	--

37-39

8. INITIAL FEV₁ and FVC
(up to 8 attempts)

	FEV ₁	FVC
1		
2		
3		
4		
5		

40-45

46-51

52-57

58-63

64-69

8.1 Number of rejected attempts

--

70

9. Best INITIAL FEV₁

--	--	--

71-73

GO TO BRONCHODILATOR CHALLENGE 4 PUFFS SALBUTAMOL INHALED AND WAIT 10-15 MINUTES, THEN PERFORM PFT'S TO ASSESS REVERSIBILITY.

BRONCHODILATOR CHALLENGE TEST

10. FEV₁ and FVC

		FEV ₁		FVC		
10.1 Record Best two technically satisfactory Manoeuvres (up to 8 attempts)	1	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	74-79
	2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	80-85
	3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	86-91
	4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	92-97

10.2 Number of rejected attempts 98

11. Best POST-BRONCHODILATOR FEV₁ 99-101

12. Did the subject experience any of the following symptoms during the challenge test?

		NO	YES	
12.1 Dry or sore throat / hoarse voice		<input type="text"/>	<input type="text"/>	102
12.2 Cough		<input type="text"/>	<input type="text"/>	103
12.3 Chest tightness/wheeze/shortness of breath		<input type="text"/>	<input type="text"/>	104
12.4 Headaches/dizziness		<input type="text"/>	<input type="text"/>	105
12.5 Other specify		<input type="text"/>	<input type="text"/>	106

Specify _____

13. General comments:

14. Technologist initial's _____ 107

15. Room temperature: _____ 108-109
(degrees celcius)

16. Lung function record appended NO YES 110

Appendix I

FE_{NO} pre-test data collection sheet

Occupational Allergy to Spices in a Spice Mill

University of Cape Town

UNIVERSITY OF CAPE TOWN
OCCUPATIONAL ALLERGY AMONG SPICE MILL WORKERS
FREDDY HIRSCH GROUP - 2008

EXHALED NITRIC OXIDE PRE-TEST DATA COLLECTION SHEET

Card 1
 1-3

Survey Number _____

A. IDENTIFICATION DATA

1. Surname _____

2. First name/s _____

3. Work number _____

4-10

4. Date of birth: Day _____ Month _____ Year _____

11-16

5. Gender: Male (1)
 Female (2)

17

6. Interviewer's initials _____

18

7. Date of interview:
 Day _____ Month _____ Year _____

19-24

8. What shift are you working this week?
 07:00 - 15:00 (1)
 15:00 - 23:00 (2)
 23:00 - 07:00 (3)

25

9.1 Date of last work shift
 Day _____ Month _____ Year _____

26-31

9.2 Which shift did you work on that day?
 07:00 - 15:00 (1)
 15:00 - 23:00 (2)
 23:00 - 07:00 (3)
 Other: _____ (4)

32

B. HEALTH PROBLEMS

Recent chest infections

1. Have you had the flu or sinusitis in the past 3 weeks?
 Yes (1)
 No (2)

33

C. SMOKING HISTORY

1. Do you smoke?

Yes (1)
No (2)

34

1.1 Have you smoked (cigarettes/tobacco) in the last hour?

Yes (1)
No (2)

35

D. ALCOHOL CONSUMPTION

1. Do you drink alcohol?

Yes (1)
No (2)

36

1.1 If yes, when have you last consumed alcohol?

1-2 hours ago (1)
1 day ago (2)
1 week ago (3)

37

1.2 How much alcohol did you consume?

38-40

E. MEDICATION USAGE

1. Are you taking any medicine/s from a doctor or clinic at the moment for asthma, and or hayfever?

Yes (1)
No (2)

41

1.1 If yes, what are you taking and when last did you take them?

Names No. of hours since last dose

42-44
 45-47
 48-50

F. GREEN VEGETABLE CONSUMPTION

1. How often do you eat the following vegetable products?

Type of product	Daily	1 to 3 times a week	1 to 3 times per month	Never
1.1 Green salad	1	2	3	4
1.2 Spinach & other green leafy vegetables	1	2	3	4

51

52

2. When did you last consume green salad and/or spinach/other green leafy vegetables?

- 1-2 hours ago (1)
- 1 day ago (2)
- 1 a week ago (3)

53

G. PHYSICAL ACTIVITY

1. Do you exercise?

- Yes (1)
- No (2)

54

2. When was the last time you exercised?

- 1-2 hours ago (1)
- 1 day ago (2)
- 1 week ago (3)

55

H. SPIROMETRY/LUNG FUNCTION TEST

1. Have you ever had a spirometry/lung function test?

- Yes (1)
- No (2)

56

2. If yes, when last did you blow into a lung function machine?

- 1-2 hours ago (1)
- 1 day ago (2)
- 1 week ago (3)
- > a week ago (4)

57

University of Cape Town

Appendix J

FE_{NO} data collection sheet

Occupational Allergy to Spices in a Spice Mill

University of Cape Town

**UNIVERSITY OF CAPE TOWN
OCCUPATIONAL ALLERGY AMONG SPICE MILL WORKERS
FREDDY HIRSCH GROUP - 2008**

EXHALED NITRIC OXIDE DATA COLLECTION SHEET

Survey Number _____

1-3

A. IDENTIFICATION DATA

1. Surname _____

2. First name/s _____

3. Work number _____

4-10

4. Date of birth: Day _____ Month _____ Year _____

11-16

5. Subject's age (in years) _____

17-18

6. Gender:

Male (1)
Female (2)

19

B. HEALTH PROBLEMS

Recent chest infections

1. Have you had the flu or sinusitis in the past 3 weeks?

Yes (1)
No (2)

20

If flu present, indicate to person that tests will not be done today. Schedule another appointment in three weeks time once flu treated.

2. Are you being treated for Tuberculosis (TB)?

Yes (1)
No (2)

21

2.1 If yes, for how long? _____ months _____ weeks

22-25

If <3 months of treatment, indicate to person that tests will not be done today. Schedule another appointment in three months time since the start of TB medication.

C. RECENT FOOD INTAKE

1. Did you have anything to eat or drink in the last hour?

Yes (1)
No (2)

26

If YES to above question, reschedule test for at least 1 hour later the same day or another date.

Appendix K

Guideline for assessing and managing medical screening results

University of Cape Town

GUIDELINE FOR ASSESSING AND MANAGING MEDICAL SCREENING RESULTS FROM SPICE MILL WORKERS – COMPILED BY PROF MOHAMED F JEEBHAY, UCT – 28 APRIL 2009

In view of the absence of international guidelines for spice dust exposure, these guidelines have been developed according to recent international guidelines published on the management of baker's asthma (2002) (Appendix 1).

1. Normal assessment

a) Criteria used in interpretation of tests by UCT medical staff

- Normal LFT (lung function test) spirometry or FeNO (fractional exhaled nitric oxide) test
- Negative Phadiotop (test for allergy to common aeroallergens found in the home environment)
- Negative specific IgE by ImmunoCAP to spice dust allergens (garlic, chili pepper, wheat)

b) Suggested management protocol to be followed by OCCUPATIONAL HEALTH staff

- Recommend regular biannual medical surveillance if working in spice-related industry i.e. spice mill.

2. Early sensitisation to spice dust

a) Criteria used in interpretation of tests by UCT medical staff

- Positive specific IgE by ImmunoCAP to spice dust allergens (garlic, chili pepper, wheat)
- No signs and symptoms of asthma or rhino-conjunctivitis
- Normal lung function test or Normal FeNO test
- (May have positive Phadiotop)

b) Suggested management protocol to be followed by OCCUPATIONAL HEALTH staff

- If first presentation, worker takes results to staff at the company clinic
- Occupational health medical/nurse practitioner screens for symptoms of allergic conjunctivitis, rhinitis, asthma, dermatitis (urticaria/eczema) and thereafter repeats this at least once a year thereafter if no symptoms
- If symptoms present the occupational health medical doctor refers worker to either the WorkHealth Occupational Diseases Clinic at Groote Schuur Hospital to confirm diagnosis (or to Prof M Jeebhay at an alternative venue to confirm diagnosis if GSH is unable to provide the follow up)
- Occupational health medical/nurse practitioner counsels worker regarding looking out for symptoms of asthma and adequate preventive measures

3. Suspected occupational rhino-conjunctivitis due to spice dust

a) Criteria used in interpretation of tests by UCT medical staff

- Reports work-related ocular/nasal symptoms
- Positive specific IgE by ImmunoCAP to spice dust allergens (garlic, chili pepper, wheat)
- Normal lung function test or Normal FeNO test
- (May have positive Phadiotop)

b) Suggested management protocol to be followed by OCCUPATIONAL HEALTH staff

- If already diagnosed as having occupational rhino-conjunctivitis, continue follow up as usual at Groote Schuur Hospital
- If first presentation, worker takes results to occupational health medical/nurse practitioner at the on-site Occupational Health Centre
- Occupational health medical doctor will make an appointment either at the WorkHealth Occupational Diseases Clinic at Groote Schuur Hospital to confirm diagnosis (or with Prof M Jeebhay at an alternative venue)

- If Occupational rhino-conjunctivitis diagnosis confirmed the doctor will:
 - Commence treatment if indicated
 - Submit claim to Compensation Commissioner (request occupational health nurse practitioner/OH sister to ensure the Employer's Report of Occupational Disease is completed)
 - Notify company (through occupational health nurse practitioner/OH sister with regard to placement in areas of low/no exposure to spice dust)
 - Areas of high exposure: packing section, blending gantry and sifter gantry
 - Areas of medium exposure: weighing and milling areas
 - Areas of low/no exposure: stores, laboratory and administration

4. Suspected occupational asthma due to spice dust

a) Criteria used in interpretation of tests by UCT medical staff

- Reports work-related chest (asthma) symptoms
- Positive specific IgE by ImmunoCAP to spice dust allergens (garlic, chili pepper, wheat)
- Reversibility of airflow obstruction with an increase of FEV1 post bronchodilator of $\geq 12\%$ **and** $\geq 200\text{ml}$ (15-30 min after four separate inhalation doses of $100\mu\text{g}$ of salbutamol)
- Abnormal FeNO (fractional exhaled nitric oxide) test: moderate increase (25-50ppb); high increase ($>50\text{ppb}$)
- (May have positive Phadiotop)

b) Suggested management protocol to be followed by OCCUPATIONAL HEALTH staff

- If already diagnosed as having occupational asthma, continue follow up as usual at Groote Schuur Hospital
- If first presentation, worker takes results to the occupational health medical/nurse practitioner at the on-site Occupational Health Centre
- Occupational health medical doctor will make an appointment either at the WorkHealth Occupational Diseases Clinic at Groote Schuur Hospital to confirm diagnosis (or with Prof Jeebhay at an alternative venue)
- If Occupational asthma diagnosis confirmed the doctor will:
 - Commence treatment if indicated
 - Submit claim to Compensation Commissioner (request occupational health nurse practitioner/OH sister to ensure the Employer's Report of Occupational Disease is completed)
 - Notify company (through occupational health nurse practitioner/OH sister with regard to placement in areas of low/no exposure to spice dust)
 - Areas of high exposure: packing section, blending gantry and sifter gantry
 - Areas of medium exposure: weighing and milling areas
 - Areas of low/no exposure: stores, laboratory and administration

5. General allergy/atopy with or without asthma

a) Criteria used in interpretation of tests by UCT medical staff

- Positive Phadiotop and negative specific IgE by ImmunoCAP to spice dust allergens (garlic, chili pepper, wheat)
- FeNO (fractional exhaled nitric oxide) test or lung function test may be abnormal if asthma present

b) Suggested management protocol to be followed by OCCUPATIONAL HEALTH staff

- If first presentation, worker takes results to occupational health medical/nurse practitioner at the company clinic or their own family doctor or day hospital if they have symptoms of asthma
- Occupational health medical doctor counsels patient regarding adequate preventive measures, symptoms of occupational asthma, placement if appropriate (if exposed to areas of high/medium dust exposure and becomes symptomatic, should be moved to areas of low/no spice dust exposure)

6. Airway inflammation (abnormal fractional exhaled nitric oxide – FeNO test)

a) Criteria used in interpretation of tests by UCT medical staff

- Abnormal FeNO (fractional exhaled nitric oxide) test: moderate increase (25-50ppb); high increase (>50ppb)
- Negative specific IgE by ImmunoCAP to spice dust allergens (garlic, chili pepper, wheat) test and phadiotop
- No other significant lung disease (from questionnaire)

b) Suggested management protocol to be followed by OCCUPATIONAL HEALTH staff

- If first presentation, worker takes results to occupational health medical/nurse practitioner at the company clinic or their own family doctor or day hospital if they have symptoms of asthma
- Occupational health medical doctor excludes recent chest infection at the time of testing, counsels patient regarding adequate general preventive measures, symptoms of occupational asthma, placement if appropriate (if exposed to areas of high/medium dust exposure and becomes symptomatic, should be moved to areas of low/no spice dust exposure)

7. Chronic obstructive airways disease

a) Criteria used in interpretation of tests by UCT medical staff

- Fixed airways obstruction with FEV1/FVC <70% with minimal airway reversibility (chronic obstructive pulmonary disease probably due to smoking, previous TB)
- Negative specific IgE by ImmunoCAP to spice dust allergens (garlic, chili pepper, wheat) test and Phadiotop
- No other significant lung disease (from questionnaire)

b) Suggested management protocol to be followed by OCCUPATIONAL HEALTH staff

- If first presentation, worker takes results to occupational health medical/nurse practitioner at the company clinic or their own family doctor or day hospital if they have symptoms of asthma
- Occupational health medical doctor counsels patient regarding smoking, adequate preventive measures, symptoms of occupational asthma, placement if appropriate (if exposed to areas of high/medium dust exposure and becomes symptomatic, should be moved to areas of low/no spice dust exposure)

Appendix 1. Recommendations from the Scandinavian workshop on the prevention of baker's rhinitis and asthma on medical screening, surveillance and individual case management:

- Asthmatics sensitized to flour or fungal alpha-amylase should change to non-bakery work.
- Asthmatics without sensitization to flour or fungal alpha-amylase should be relocated to less exposed bakery tasks.
- Bakers with rhinitis and sensitization should be investigated closely and relocation to less exposed tasks should be considered.
- Bakers sensitized to flour or fungal alpha-amylase but without respiratory symptoms should be re-examined annually.
- Bakers with rhinitis only but without sensitization to bakery allergens do not warrant re-examination unless symptoms worsen.

University of Cap Town

Appendix L

Medical report of results

University of Cap Town

UNIVERSITY OF CAPE TOWN



OCCUPATIONAL AND ENVIRONMENTAL HEALTH RESEARCH UNIT

School of Public Health & Family Medicine

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UNIVERSITY OF CAPE TOWN OCCUPATIONAL ALLERGY AMONG SPICE WORKERS FREDDY HIRSCH GROUP – 2008/2009

MEDICAL REPORT

Date _____

Name _____

This is the report of the medical evaluation and tests conducted on you by the medical staff from the University of Cape Town, as part of the project on occupational spice allergy.

1. Presence of **work-related** symptoms reported by you on **questionnaire**.

Eye/Nose	Chest	Skin	Questionnaire completed
<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	<input type="checkbox"/> Yes
<input type="checkbox"/> No	<input type="checkbox"/> No	<input type="checkbox"/> No	<input type="checkbox"/> No

2. **Lung Function Test Results**

Test not done Normal Abnormal

If Abnormal Specify: Reversible Airway Obstruction [Probable Asthma]

Fixed Airway Obstruction (FEV₁/FVC<70%)
[Probable Chronic Obstructive Airways Disease]

3. **Exhaled Nitric Oxide (FeNO) Test Results**

Pre-shift day 1:

Normal (<25ppb) Moderately increased (25-50ppb) High (>50ppb)

Post-shift day 1:

Normal (<25ppb) Moderately increased (25-50ppb) High (>50ppb)

Pre-shift day 2:

Normal (<25ppb) Moderately increased (25-50ppb) High (>50ppb)

4. **Phadiotop blood test** results: (general allergy to common inhalable allergens found in the in-door and out-door home environment)

Test not done Normal Abnormal (Atopic)

5. **Specific IgE antibody blood test** results: (allergens in spice dust: garlic, chilli pepper and wheat)

Test not done Normal Abnormal

If Abnormal Specify: _____

6. OVERALL COMMENTS

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

- The results were normal.
- The results indicate early sensitization and suspected allergy to spice dust. Please make an appointment with the occupational health nurse/doctor for further monitoring on a regular (at least once a year) basis.
- The results indicate that you have suspected/confirmed occupational rhinoconjunctivitis (eye or nose problems) due to spice dust (garlic, chilli pepper and or wheat). Please make an appointment with the occupational health nurse/doctor so that you may be referred for further evaluation.
- The results indicate that you have suspected/confirmed occupational asthma due to spice dust (garlic, chilli pepper and or wheat). Please make an appointment with the occupational health nurse/doctor so that you may be referred for further evaluation.
- The results indicate that you may have suspected/confirmed allergy to common inhalable allergens in the home environment. Please consult your family doctor should you have hayfever or chest symptoms and if you are not on any treatment.
- Your high exhaled nitric oxide levels may be due to a recent chest infection reported by you at the time of testing or the presence of airway inflammation associated with asthma.
- The results indicate that you may have chronic obstructive airways disease. Please consult your family doctor for further evaluation should you have chest symptoms.

We are including 3 copies of this report to show to your family medical doctor and/or to the company occupational health nurse/doctor so that they may be able to assist you with medical treatment or recommend changes to your work activities should this be necessary.

Please do not hesitate to contact Prof M F Jeebhay (Telephone: 021-4066309) or Dr A van der Walt (Cell: 0833277353) should you have any queries or require more detailed results of the investigations done on you.

Yours faithfully

Prof M F Jeebhay

Appendix M

Photographs

Spice mill production area

University of Cape Town

Appendix M

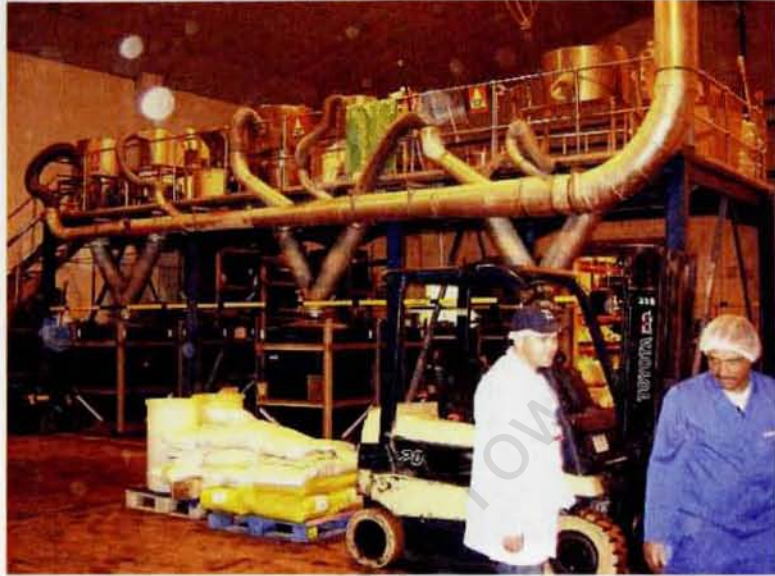


FIGURE 1: Depicting the infrastructure of local exhaust ventilation (LEV) provided at the Sifter Gantry.



FIGURE 2: Showing typical semi-enclosed hoods provided at the charging positions of the Sifter Gantry and Blending Gantry to contain capture and remove dust before being distributed into the general working environment.



FIGURE 3: Showing the infrastructure of local exhaust ventilation (LEV) provided at packing with normal plain duct hoods at the bagging positions.

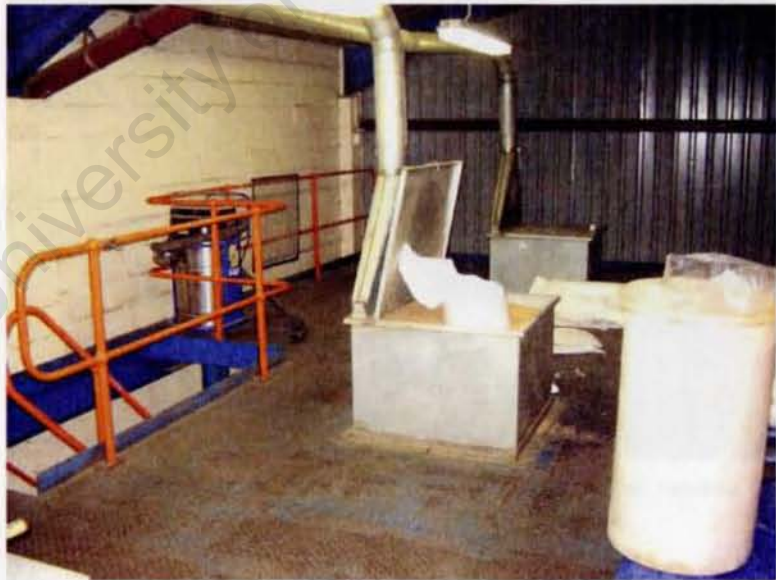


FIGURE 4: Showing the extraction provided at the Milling Gantry charging position which was not in use due to loss of product when the system is functioning.



FIGURE 5: Depicting the dusty atmosphere during charging performed at the Blending Gantry.



FIGURE 6: Showing operator with sampling pump on the waist and filter cassettes positioned in the breathing zone for performing personal sampling.



FIGURE 7: Bagging position of the Dowatech packing machine.



FIGURE 8: Hand packing operations in progress. Note the dust being generated from the process to which the employees are exposed.