

OCCUPATIONAL ALLERGY AND ASTHMA IN TOBACCO FARMERS: A REVIEW OF LITERATURE

Dorothy Ngajilo | MD, MMed

Shahieda Adams | MBChB, MMed, PhD

Mohamed F Jeebhay | MBChB, MPhil (Epi), MPH (Occ Med), PhD

Occupational Medicine Division, School of Public Health and Family Medicine, University of Cape Town

Email | dorongajilo@yahoo.com

ABSTRACT

For decades, multinational tobacco companies and their associated organisations have claimed that tobacco production brings prosperity to farmers and farming communities, particularly in lower-middle-income countries. This is contrary to emerging research that shows tobacco production not only increases the economic burden of workers but is also responsible for a number of health problems. This article reviews current knowledge on occupational allergy, asthma and related respiratory diseases among tobacco farmers from various literature sources published between 1960 and 2018. The review found that workers in the tobacco industry are exposed to a large spectrum of potentially hazardous chemical and biological agents leading to allergic and non-allergic respiratory disease. Further research needs to explore in greater detail – using more objective markers – the exposure to tobacco dust, nicotine and pesticides, and their interaction in causing respiratory disease in this group of workers.

INTRODUCTION

Tobacco (*Nicotiana tabacum*) is cultivated throughout temperate and tropical regions worldwide, including North and South America, Europe, Africa and Asia.¹ For decades, multinational tobacco companies and their associated organisations have claimed that tobacco production brings prosperity to farmers and farming communities, particularly in the lower-middle-income countries (LMICs).^{2,3} This is contrary to emerging research that shows tobacco production not only increases the economic burden of workers but is also responsible for a number of health problems. Workers in the tobacco industry are exposed to a large spectrum of potentially hazardous agents. These have been associated with several recurrent acute and sub-acute symptoms and potentially unknown long-term and chronic effects, particularly on the respiratory and nervous systems.^{2,4}

Recent decades have seen a steady shift of tobacco production from high-income countries (HICs) to LMICs.⁵ The negative health impacts of this shift are accentuated in the LMICs due to the lack of occupational health regulation, poverty as well as poor access to healthcare.¹

This article reviews current knowledge on occupational allergy and asthma among tobacco farmers. MEDLINE, Google Scholar and SCOPUS databases were searched to identify relevant

articles from 1960 to 2018. The key words used included: asthma, allergy, sensitisation, respiratory, pulmonary, immunological, rhinitis, work related, occupational, tobacco, *Nicotiana tabacum*, dust, nicotine, pesticides, organophosphates, neonicotinoids, growth regulators, bacteria, fungi, endotoxin, (1–3) β -D glucan, allergens and mites. The review articles found in the process were also examined for additional and earlier citations.

THE TOBACCO WORKING PRACTICE AND HIGH-RISK OCCUPATIONAL EXPOSURE SETTINGS

The tobacco farming process varies depending on the specific type of tobacco plant grown. Among the several varieties of tobacco, the most common are Virginia, Burley and Oriental.⁶ Whereas the methods of cultivating, harvesting and curing these plants differ, specific health risks to tobacco farmers are common to all tobacco cultivation processes.¹ Figure 1 depicts the typical tobacco-working process.

In summary, the tobacco plant begins its life cycle as a seed sown and carefully tended in specially constructed seedbeds in nurseries for two months in order to produce seedlings. The seedlings are then transplanted into the fields. Here they are tended carefully for two to three months prior to being harvested. Between transplantation and harvesting, farmers monitor growth, carry out pest and disease control and remove flowers (topping the plants) to ensure heavier and higher quality leaves.⁷ Tobacco may be harvested either leaf by leaf

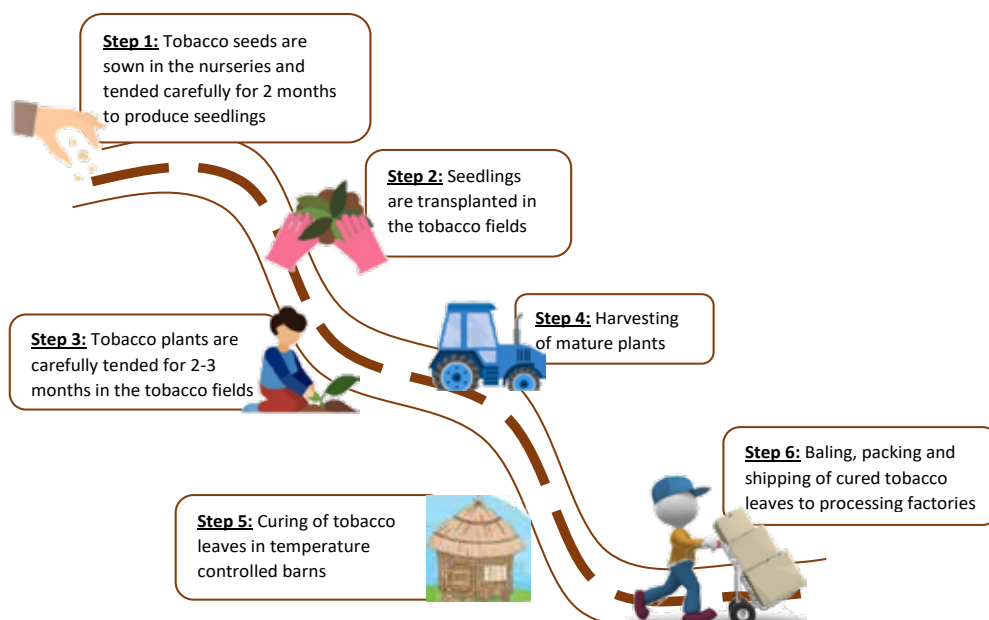


Figure 1: Typical tobacco farming work process

(Virginia and Oriental) or as the whole plant (Burley)(see Figure 2a). Leaf-by-leaf harvesting presents a higher risk of exposure to occupational agents present in tobacco plant compared to whole-stalk harvesting.⁴ Post-harvest activities include curing (drying of tobacco leaves, often with wood smoke) (see Figure 2b), baling (compacting leaves into bales), sheeting (tying tobacco into burlap sheets), packing and shipping to processing factories.²

The abovementioned farming activities are associated with exposure to different occupational hazards that may cause respiratory disease among tobacco farmers. Table I summarises these activities and their associated potential respiratory hazards.

On the one hand, tobacco cultivation and harvesting exposes farmers to pesticides, fertilisers, growth regulators and nicotine (see Figure 2a).⁸ On the other hand, tobacco curing carries high risk of exposure to tobacco dust, ammonium, nicotine, carbon

monoxide, carbon dioxide, furanic aldehyde, moulds and fungi (see Figure 2b). The curing process which usually occurs in airtight barns at a constant temperature level (for 72–96 hours), may take up to eight weeks. This requires farmers to constantly enter curing barns to add leaves and branches to an open fire. During this period, farmers inhale large quantities of smoke, which increases their risk of acquiring respiratory disease.

After curing, the tobacco leaves are stored in closed spaces, usually inside farmers' homes due to lack of designated storage spaces. This practice further increases the risk of inhalation of hazardous tobacco dust, fungi and mould.²

The lack of adequate control measures including personal protective equipment (PPE) such as respirators, gloves and boots, due to the high cost of this equipment or to the fact that they are not adapted to a tropical climate, makes agricultural workers vulnerable to acute and chronic poisoning caused by pesticides applied during different stages of the tobacco production process.⁷



Figure 2a: Tobacco-leaf harvesting (source: <https://www.herald.co.zw/changing-fortunes-of-former-farm-workers-in-zimbabwe/>)



Figure 2b: A tobacco-curing barn (personal archives)

TABLE I: TASKS ASSOCIATED WITH POTENTIAL EXPOSURE TO OCCUPATIONAL AGENTS THAT MAY CAUSE RESPIRATORY DISEASE IN TOBACCO FARMERS

TASKS	DESCRIPTION OF DUTIES	SOURCES OF HAZARDOUS EXPOSURE
Cultivation	Seedling preparation, transplantation in fields and tending the tobacco plants.	Nicotine from fresh tobacco leaves, fertilisers, insecticides, herbicides, ripening agents and growth regulators. ⁸
Harvesting	Selecting mature green tobacco leaves, cutting leaves at ground level, loading leaves onto wagons, and transferring leaves to curing barns.	Nicotine from fresh tobacco leaves and pesticides. ⁸
Curing	Drying green tobacco leaves in curing barns, often using wood smoke. The leaves are fermented by moistening and leaving them in rooms for several months. Dried leaves are then bundled, pressed, and shipped to the processing factories.	Nicotine from fresh tobacco leaves, tobacco dust, volatile substances (nicotine, ammonium, carbon monoxide and carbon dioxide, furanic aldehyde), mould, fungi, endotoxins, mites. ⁸

CHEMICAL AND BIOLOGICAL HAZARDS PRESENT IN TOBACCO WORK

Tobacco farmers are exposed to a complex mixture of chemical and biological agents. These are described in detail below.

CHEMICAL HAZARDS

Tobacco farming is a highly chemically intensive process. As a monocrop, tobacco plants are highly susceptible to pests and diseases and as a result, successful crop requires multiple application of large quantities of agrichemicals.^{2,9} These include pesticides (fumigants, insecticides, herbicides and fungicides) and growth regulators (ripening agents and growth inhibitors) that are applied to the tobacco plant during different stages of growth.⁹ In addition, tobacco farming requires intensive use of chemical fertilisers. This is due to the tobacco plant depleting soil fertility more rapidly than other crops because it absorbs more nitrogen, phosphorus and potassium from the soil.² Furthermore, tobacco farmers are exposed to nicotine through skin absorption when handling green tobacco leaves during the tobacco harvest. As a result these farmers have been shown to have elevated levels of cotinine in urine, blood and saliva.^{10–12}

A Pakistani study reported a high concentration of neonicotinoid, carbamate, pyrethroid and organochlorine pesticide residues above the acceptable daily intake (ADI) for humans in the blood of tobacco farmers.¹³ These included methomyl (63%), thiodicarb (56%), cypermethrin (62%), imidacloprid (49%), methamidophos (32%) and endosulfan (27%). In this study butyrylcholinesterase (BChE) activity was found to be significantly decreased in the pesticide exposed farmers compared to controls ($p = <0.001$). Another study conducted in the same population reported mild (33%) to moderate (11%) pesticide poisoning signified by depression of plasma cholinesterase (PChE) levels. The majority of farmers in this group reported not using any PPE and lacked formal training in safe pesticide handling.¹⁴ Studies quantifying nicotine exposure have reported urinary nicotine in the range of 120–160 ng/mL [reference: 0–2 ng/mL] and cotinine 88–1 808 ng/mL [reference: 0–5 ng/mL].^{11,12,15}

BIOLOGICAL HAZARDS

Tobacco farmers are also exposed to tobacco dust, which contains various immunologically active as well as toxic substances.¹⁶ These include bacteria, endotoxins, mould, fungal spores, pollen, mites and insects.^{17,18} Inhalation can occur when handling dry tobacco leaves during curing, baling, packing and loading for transportation.⁷ Furthermore, the practice of storing

tobacco leaves in closed spaces inside farmers' homes due to the lack of designated storage spaces further increases the risk of tobacco-dust inhalation.² A Zimbabwean study reported levels of respirable tobacco dust among tobacco farm workers of $19.13 \pm 10.82 \text{ mg/m}^3$,¹⁹ which is much higher than the occupational exposure limit for inhalable dust (10 mg/m^3).

RESPIRATORY HEALTH EFFECTS ASSOCIATED WITH TOBACCO WORK

The respiratory system is the most common site of injury when exposed to chemical and biological airborne pollutants.²⁰ In tobacco farming, chronic exposure to occupational agents has been shown to be associated with rhinitis, asthma and asthma-like symptoms, allergic alveolitis, chronic obstructive pulmonary disease (COPD) and other non-specific pulmonary symptoms (see Table II).

RHINITIS

Studies have reported the prevalence of rhinitis-like symptoms (nasal congestion, runny nose and itchiness around eyes and nose) among tobacco farmers to be between 8% and 34%.^{20,21} These symptoms have been attributed to occupational and non-occupational exposures. Kearney et al reported a high prevalence of runny stuffy nose (34%), nasal allergies (17%) and sinusitis/sinus problems (12%) among migrant tobacco farmers related to poor indoor housing conditions.²⁰ On the other hand, occupational factors such as harvesting or topping tobacco plants were also associated with runny, stuffy nose in the same study.

ASTHMA

Although the prevalence of doctor diagnosed asthma among tobacco farmers has been reported to be 3%,²⁰ a higher prevalence of asthma-like symptoms such wheezing (3–24%), chest tightness (17%), coughing (7–18%) and dyspnoea (6–28%) have been reported. These were, however, less than the prevalence of upper-airway symptoms. A case report of a patient with features suggestive of occupational asthma due to dried tobacco leaves exposure has also been reported.²² In this case, sensitisation to tobacco leaf was confirmed by a positive skin-prick test (SPT) using an extract of dried Paraguay Bell leaf. A specific bronchial-challenge test using the same tobacco, not contaminated by mould, was associated with a 23% fall in FEV₁. This suggested an IgE-dependent sensitisation to tobacco leaf as one of the mechanisms for occupational asthma in tobacco farm workers.

TABLE II: EPIDEMIOLOGICAL STUDIES OF WORK-RELATED ASTHMA AND OTHER RESPIRATORY SYMPTOMS IN TOBACCO FARMERS

STUDY – AUTHOR, YEAR	COUNTRY	STUDY DESIGN	SUBJECTS N (M:F)	RESPIRATORY SYMPTOM/ DISEASE PREVALENCE (%)	LUNG-FUNCTION TESTS (MEAN/ ABNORMALITY PREVALENCE)	RISK FACTORS – HOST AND ENVIRONMENTAL	TOOLS USED
Cargin et al, 2016 ²⁸	Brazil	Cross-sectional	100 (100:0)	- throat irritation: 3% - cough: 1%	ND	<u>Environmental</u> Increased employment duration	questionnaire
Fiori NS, 2015 ³⁰	Brazil	Cross-sectional	2469 (59:41)	wheezing in the past 12 months: 11%	ND	Men: <u>Host</u> - smoking: RR = 1.53 (95% CI 1.10–2.13) - age >55 years: RR = 1.71 (p-trend = 0.022) <u>Environmental</u> - exposure to dry tobacco dust: RR = 1.59 (p-trend 0.039) - strenuous work: RR = 1.72 (95% CI 1.14–2.61) - pesticide use >10 days per month: RR = 2.71 (95% CI 1.56–4.71) ≥6GTS episodes: RR = 3.12 (p-trend <0.001) - lifting sticks with tobacco leaves to the curing barns: RR = 1.48 (p-trend = 0.024) - harvesting lower tobacco leaves (protective): RR = 0.35 (p-trend <0.001) Women: <u>Host</u> - family history of asthma: RR = 2.02 (95% CI: 1.3–3.15) <u>Environmental</u> - tying hands of tobacco: RR = 3.89 (95% CI 1.17–12.94) - strenuous work: RR = 1.76 (95% CI 1.22–2.54) ≥30 years of exposure to pesticides: RR = 2.32 (p-trend = 0.002) - exposure to chemical disinfectants: RR = 1.54 (95% CI 1.00–2.35) ≥6GTS episodes in previous year: RR = 2.29 (p-trend = 0.005) - harvesting lower tobacco leaves (protective): RR = 0.46 (p-trend = 0.018)	questionnaire
Kearney et al, 2014 ²⁰	United States	Cross-sectional	352 (100:0)	- runny or stuffy nose: 34% - sinusitis/sinus problem: 12% - nasal allergies: 17% - wheeze: 11% - coughing up phlegm: 17% - chest tightness: 17% - woken up with tight chest: 17% - woken up with dyspnoea: 14% - doctor diagnosed asthma: 3%	FEV ₁ : 3.91 ± 0.69 L FEV ₁ <predicted: 5% FEV ₁ /FVC%: 82.90 ± 2.22	<u>Environmental</u> - mould in the sleeping room and coughing up phlegm (p = 0.026) - presence of cockroach infestation in the sleeping room and chest tightness (p = 0.055) - presence of mould and asthma (p = 0.008) - pesticides in the home and tightness of chest (p < 0.001) - use of tobacco and coughing up phlegm (p = 0.013)	- questionnaire - spirometry
Mirabelli et al, 2011 ²¹	United States	Cross-sectional	122 (100:0)	- ever wheezing: 24% - wheezing in the last 12 months: 16% - wheezing in the last month: 8% - wheezing in the past three days: 3% - woken by coughing: 7% - woken up with dyspnoea: 6% - itchy eyes: 11% - runny or stuffy nose: 8% - nasal allergies, including hay fever: 19%	ND	<u>Environmental</u> <i>Higher odds of wheezing:</i> - topping tobacco: OR = 2.4 (95% CI: 0.9–6.3) - barring or baling tobacco: OR = 1.7 (95% CI: 0.6–5.4) <i>Lower odds of wheezing:</i> - harvesting activities: OR = 0.3 (95% CI: 0.1–1.0)	questionnaire

TABLE II: EPIDEMIOLOGICAL STUDIES OF WORK-RELATED ASTHMA AND OTHER RESPIRATORY SYMPTOMS IN TOBACCO FARMERS

STUDY – AUTHOR, YEAR	COUNTRY	STUDY DESIGN	SUBJECTS N (M:F)	RESPIRATORY SYMPTOM/ DISEASE PREVALENCE (%)	LUNG-FUNCTION TESTS (MEAN/ ABNORMALITY PREVALENCE)	RISK FACTORS – HOST AND ENVIRONMENTAL	TOOLS USED
Van Minh et al, 2009 ³¹	Vietnam	Cross-sectional	2120 1065 tobacco farming (50:50) 1055 controls (48:52)	• dyspnoea: 24%	ND	NR	• questionnaire
Osim et al, 1998 ¹⁹	Zimbabwe	Cross-sectional	50 (100:0) 20 tobacco farming, 30 controls	NR	Workers: FVC: 3.28 ± 0.51 L FEV ₁ : 2.68 ± 0.74 L PEFR: 6.41 ± 2.08 L/min Controls: FVC: 3.97 ± 0.83 L FEV ₁ : 3.09 ± 0.71 L PEFR: 8.62 ± 2.74 L/min	<u>Environmental</u> • tobacco flue curing activities • stacking tobacco leaves in bales • increased employment duration and reduced FVC: ($r = -0.74$; $p = <0.01$)	• questionnaire • spirometry
Ghosh et al, 1980 ²⁷	India	Cross-sectional	440 290 tobacco farming (70:30) 150 controls (74:26)	Workers: • cough: 19% • cyspnoea: 29% • Emphysema: 12% Controls: • cough: NR • dyspnoea: NR • Emphysema: 8%	Workers: VC: 2.66 ± 0.06 L FEV ₁ %: 64.10 ± 1.17 L Controls: VC: 2.92 ± 0.007 L FEV ₁ %: 72.00 ± 1.104 L	<u>Host</u> • smoking and reduced VC ($p = <0.01$)	• questionnaire • spirometry

ND=Not Done, NR= Not reported, FEV₁= Forced Expiratory Volume in one second, FVC=Forced Vital Capacity, VC=Vital Capacity, PEFR= Peak Expiratory Flow Rate, GTS=Green Tobacco Sickness

ALLERGIC ALVEOLITIS (TOBACCO WORKERS' LUNG)

Tobacco farmers are known to be at risk of developing allergic alveolitis due to organic tobacco dust exposure. A Russian study of 510 allergic alveolitis patients reported tobacco farm workers to have a more severe disease compared to wood and cotton workers, with fungal infection exerting a substantial effect on the clinical course of the disease.²³ An analysis of chest radiographic changes of 143 tobacco farmers with allergic alveolitis revealed three clinical variants of the disease, namely, obstructive bronchitis, bronchial asthma and recurring pneumonia, with all workers demonstrating sensitisation to tobacco antigen.^{24,25} Among these three clinical variants, the obstructive pattern associated with pulmonary hyperinflation was the predominant abnormality in the lung-function parameters.²⁶

SPIROMETRIC ABNORMALITIES

An Indian study reported a higher prevalence of emphysema (12%) among tobacco growers when compared to unexposed controls (8%).²⁷ Growers compared to controls, were also found to have significantly lower mean vital capacity (VC) (2.66 ± 0.06 vs 2.92 ± 0.01 L) and FEV₁/FVC% values (64.10 ± 1.17 vs 72.00 ± 1.10 L). In another study of US tobacco farmers, spirometric findings suggestive of an obstructive picture (FEV₁ outside the normal range of predicted values) were reported in 5% of workers.²⁰ However, all workers in this study had an FEV₁/FVC ratio above 70% (82.90 ± 2.22), a finding that was attributed

to a possible healthy worker effect. Similarly, Zimbabwean tobacco growers exposed to flue curing and stacking tobacco leaves were shown to have a significantly lower mean FEV₁ (2.68 ± 0.74 L) and FVC (3.28 ± 0.51 L) values compared to controls (3.09 ± 0.71 L and 3.97 ± 0.83 L) respectively.¹⁹ These findings suggest that both obstructive and restrictive lung-function abnormalities are present in tobacco farmers.

OTHER RESPIRATORY SYMPTOMS AND DISEASES

Several non-specific respiratory symptoms have been reported among tobacco farmers. These include cough, eye irritation, phlegm, throat irritation and sinusitis/sinus problems.^{20,21,28} In addition, a case of eosinophilic pneumonia in a Japanese tobacco harvester has also been documented.²⁹ The patient demonstrated eosinophilia on full blood count (FBC) and bronchoalveolar lavage (BAL) fluid with a negative serology for parasitic infection. She had a positive skin scratch test using tobacco leaf and leaf extract, and a biopsy of the dermis on the patch tested area revealed an eosinophilic infiltration. Her chest computed tomography (CT) showed patchy consolidation. The investigators attributed the patient's condition to tobacco leaf exposure via inhalation while she was harvesting and sorting tobacco leaves.

This wide range of symptoms emphasises the complexity of pathophysiological mechanisms through which occupational

TABLE III: CASE REPORTS OF WORK-RELATED RESPIRATORY DISEASE IN TOBACCO FARMERS

STUDY	COUNTRY	OCCUPATION	RESPIRATORY HEALTH EFFECTS	DURATION OF EXPOSURE PRIOR TO SYMPTOMS	CONFIRMATION DIAGNOSIS OF ALLERGY OR ASTHMA
Yoshioka et al, 2011 ²⁹	Japan	Tobacco harvester	Eosinophilic pneumonia	Two months	- eosinophilia on FBC with negative serology for parasitic infection - patchy consolidation on chest CT - marked eosinophilia on BAL fluid - positive skin-scratch test using tobacco leaf and leaf extract - eosinophilic infiltration of the dermis on biopsy of the patch-tested area
Wendling et al, 1994 ²²	France	Tobacco farmer	Occupational asthma	NR	SIC with 23% drop in FEV₁ after 20 minutes of sorting dry tobacco leaves

BAL= Broncho-alveolar Lavage, CT= Computed Tomography, FBC=Full Blood Count, FEV₁= Forced Expiratory Volume in one second, NR= Not reported, SPT= Skin Prick Test

exposures present in tobacco work may cause respiratory disease.

PATHOPHYSIOLOGICAL MECHANISMS

RHINITIS

Tobacco dust exposure is responsible for rhinitis symptoms among tobacco workers. A study done among workers chronically exposed to tobacco dust revealed loss of cilia and squamous epithelial metaplasia in the nasal mucosa of tobacco workers when compared to unexposed controls. However, these workers failed to demonstrate hyper-eosinophilia in nasal swabs and their tobacco specific IgE and total IgE levels did not differ from controls. This suggested that rhinitis associated with tobacco-dust exposure may be mediated largely through irritant rather than allergic mechanisms.³²

ASTHMA

Both allergic and non-allergic mechanisms have been implicated in asthma causation among workers exposed to tobacco dust. Work related asthmatic symptoms were reported in a female tobacco worker.³³ In this worker, occupational asthma was confirmed by positive SPT and specific inhalation challenge tests using tobacco dust, suggesting an allergic mechanism as the cause for the asthma.

In vitro studies have shown tobacco dust to cause concentration-dependent contractions of guinea pig trachea.^{34,35} Using tobacco-dust extracts containing significant quantities of bacterial components (e.g. endotoxin), Schachter et al demonstrated that the constrictor activity of the tobacco-dust extract is mainly in its non-lipid, low molecular weight fraction (<10 kDa).³⁴ The study suggested that tobacco dust causes airway smooth muscle constriction mainly through non-immunologic mechanisms involving a variety of airway mediators and possibly cholinergic receptors. In a follow-up study, Schachter et al demonstrated greater contractile response to tobacco-dust extract in guinea pig tracheas pre-sensitised with ovalbumin than tracheas that were not pre-sensitised.³⁵ This finding suggested that pre-sensitisation with an unrelated antigen may enhance the response to an occupational agent.

ALLERGIC ALVEOLITIS

Immune mediation may be one of the pathophysiological mechanisms in the development of tobacco worker's lung. A Finnish study conducted among workers exposed to tobacco dust demonstrated serum antibodies against *M faeni*, *T vulgaris*, *A fumigatus* and *A umbrinosus*.³⁶ In this study, the prevalence of antibodies was significantly higher among workers with respiratory symptoms and fibrotic radiographic signs than among other workers. *Aspergillus* species from tobacco mould appeared to be the main antigen causing tobacco worker's lung. It is also postulated that exposure to tobacco dust and its constituents may have direct toxic effects on pulmonary macrophages leading to the release of lysosomal enzymes and other immune mediators that cause pulmonary inflammation with subsequent chronic allergic alveolitis.¹⁸ These findings indicate that raw tobacco dust and its constituents may either cause allergic or toxic reactions or both, leading to the development of allergic alveolitis.

HOST-ASSOCIATED RISK FACTORS FOR RESPIRATORY DISEASE

There are few host-associated factors associated with respiratory disease among tobacco farmers.

GENETICS

The role of genetics in the development of asthma and other work-related respiratory illnesses among tobacco farmers has not been well documented. A positive history of asthma in one or both parents was associated with an increased risk of wheezing among female tobacco farmers in a Brazilian study (RR = 2.02).³⁰ This is similar to the findings for adult onset asthma, for which parental asthma has been shown to be a risk factor.³⁷

AGE

Increasing age has been shown to increase the risk of wheezing among Brazilian tobacco farmers.³⁰ In this group of workers, males aged 55 or above were shown to have the greatest risk of reporting wheeze in the past year (RR = 1.71). The direct association between age and wheezing in male tobacco growers may be attributed to cumulative exposure to cigarette smoke.³⁸ No association was found between increasing age and wheezing among females, possibly due to the lower prevalence of smoking.³⁰

SMOKING

Current smoking among males was associated with wheezing in Brazilian tobacco farmers (RR = 1.53).³⁰ Both animal and human studies have demonstrated cigarette smoke inhalation to induce acute bronchoconstriction.^{39–42} Furthermore, it has been suggested that simultaneous and persistent exposure to smoking and airborne allergens may have an additive or synergistic effect on the occurrence of adult-onset asthma.⁴³

OCCUPATIONAL RISK FACTORS FOR RESPIRATORY DISEASE

MODE OF EXPOSURE

Both inhalational and dermal routes appear to be important. In a study of Brazilian tobacco farmers, inhalation of dry tobacco dust was associated with an increased risk of wheezing (RR = 1.59).³⁰ This study also found that individuals with multiple green tobacco sickness (GTS) episodes in the past year were at a higher risk of developing wheeze (men: RR = 3.12, women RR = 2.29). GTS results from acute nicotine poisoning caused by dermal absorption of nicotine from mature tobacco plants with subsequent neurotoxic symptoms including headaches, dizziness, nausea and vomiting. With GTS being caused by dermal absorption of nicotine, this finding suggests a possible role of dermal exposure for occupational asthma in tobacco workers, as has been recently reported in some occupational settings.⁴⁴

EXPOSURE TO CHEMICAL AGENTS RELATED TO TOBACCO WORK

Chronic pesticide exposure in tobacco farming has been shown to increase the risk of wheezing among tobacco farmers. In a Brazilian study, the occurrence of wheezing was associated with pesticide use for more than ten days a month in men (RR = 2.71) and in females with long duration (>30 years) of use (RR = 2.32).³⁰ The same study also found exposure to chemical disinfectants to increase the risk of wheeze (RR = 1.54).

While occupational exposures play an important role in the development of respiratory symptoms, the effect of domestic exposure particularly in tobacco farmers living on farms is also important.^{2,20} In a US study of Latino migrant farm workers involved in tobacco farming, mould exposures in the home was associated with phlegm production and asthma ($p < 0.05$).²⁰ The study also identified other domestic risk factors for respiratory diseases including cockroach infestation and pesticide exposure in the home ($p < 0.05$). These findings highlight the need to address domestic exposures when designing interventions for reducing occupational exposures.

HIGH-RISK JOBS/TASKS

Various high-risk jobs and tasks have been implicated in the development of respiratory disease among tobacco farmers. Fiori et al reported an increased risk of wheezing among female farmers involved in lifting sticks with tobacco leaves in the curing

barns (RR = 1.48), and male farmers involved in tying hands of tobacco (RR = 3.89).³⁰ Harvesting the lower tobacco leaves appeared to be associated with a lower risk (females RR = 0.35 vs males RR = 0.46), which has also been reported among migrant Latino tobacco farm workers (RR = 0.3).²¹ Being a cross-sectional study, these findings suggest a possible healthy worker effect since tobacco harvesting carries a higher risk of exposure to nicotine and pesticides, as it requires substantial physical effort, takes place in a hot and humid environments and requires significant leaf handling.³⁰ Other high-risk tasks reported include topping, burning, flue curing and stacking of tobacco leaves into bales.^{19,21} Furthermore, strenuous work has also been shown to increase the risk of wheeze in male (RR = 1.72) and female (RR = 1.76) tobacco-farm workers.³⁰

LEVEL OF EXPOSURE

In-vitro studies have demonstrated a dose-response relationship between exposure to tobacco-dust extract and development of possible bronchoconstriction in guinea pigs.^{34,35} On the other hand, increased employment duration has been associated with a decrease in FVC ($r = -0.74$; $p < 0.01$) among Zimbabwean tobacco farmers.¹⁹ Similarly, Cargnin et al reported increased employment duration to be associated with respiratory symptoms including throat irritation and cough among tobacco farmers.²⁸

CONCLUSION

This review confirms that tobacco farmers are at increased risk of allergic and non-allergic respiratory disease as a result of exposure to different chemical and biological hazards related to tobacco farming. Future studies are needed to address the following issues in greater depth:

- Quantification of exposure to tobacco dust, nicotine and pesticides particularly in tobacco farmers from LMICs.
- Improved identification of asthma phenotypes using objective measures.
- Investigation of the interaction between pesticides, nicotine and tobacco dust in causing respiratory disease.
- Investigating the long-term health effects of mixed exposures in tobacco work.
- Identification of the effects of newer pesticide groups such as neonicotinoids, in causing respiratory disease in tobacco farmers.
- Investigating exposure–response relationships in epidemiological studies of tobacco workers.

DECLARATION OF CONFLICT OF INTERESTS

The authors declare no conflict of interest

ACKNOWLEDGEMENT

The University of Cape Town and the Organization for Women in Science for the Developing World (OWSD) are gratefully acknowledged for the doctoral fellowship to D Ngajilo.

REFERENCES

1. Arcury TA, Quandt SA. Health and social impacts of tobacco Pproduction. *J Agromedicine* 2006;11(3–4):71–81.
2. Lecours N. The harsh realities of tobacco farming: a review of socioeconomic, health and environmental impacts. In: Leppan W, Lecours N, Buckles D, editors. *Tobacco control and tobacco farming: separating myth from reality*. Ottawa: Anthem Press; 2014. p. 99–137.
3. Kagaruki LK. Invited commentary. *Tob Control* 2012;21(2):196–197.
4. Schmitt NM, Schmitt J, Kouimintzis DJ, Kirch W. Health risks in tobacco farm workers—a review of the literature. *J Public Heal* 2007;15(4):255–264.
5. Lecours N, Almeida GEG, Abdallah JM, Novotny TE. Environmental health impacts of tobacco farming: a review of the literature. *Tob Control* 2012;21(2):191–196.
6. Norman A, Davis DL, Nielsen MT. *Tobacco: production, chemistry and technology*. Blackwell Science, London; 1999.
7. Riquinho DL, Hennington EA. Health, environment and working conditions in tobacco cultivation: a review of the literature. *Cien Saude Colet* 2012;17(6):1587–1600.
8. Bonamonte D, Vestiita M, Filoni A, Mastrodonardo M, et al. Tobacco-induced contact dermatitis. *Eur J Dermatol* 2016;26(3):223–231.
9. Lecours N, Almeida GEG, Abdallah JM, Novotny TE. Environmental health impacts of tobacco farming: a review of the literature: Table 1. *Tob Control* 2012;21(2):191–196.
10. Gehlbach SH, Williams WA, Perry LD, Freeman JI, et al. Nicotine absorption by workers harvesting green tobacco. *Lancet* 1975;305(7905):478–480.
11. D'Alessandro A, Benowitz NL, Muzi G, Eisner MD, et al. Systemic nicotine exposure in tobacco harvesters. *Arch Env Heal* 2001;56(3):257–263.
12. Arcury TA, Laurienti PJ, Talton JW, Chen H, et al. Urinary cotinine levels among Latino tobacco farmworkers in North Carolina compared to Latinos not employed in agriculture. *Nicotine Tob Res* 2016;18(6):1517–1525.
13. Khan DA, Bhatti MM, Khan FA, Naqvi ST, Karam A. Adverse effects of pesticides residues on biochemical markers in pakistani tobacco farmers. *Int J Clin Exp Med* 2008;1(3):274–282.
14. Khan DA, Shabbir S, Majid M, Ahad K, et al. Risk assessment of pesticide exposure on health of Pakistani tobacco farmers. *J Expo Sci Env Epidemiol* 2010;20(2):196–204.
15. Trapé-Cardoso M, Bracker A, Dauser D, Oncken C, et al. Cotinine levels and green tobacco sickness among shade-tobacco workers. *J Agromedicine* 2005;10(2):27–37.
16. Ignacak A, Guzik TJ, Górski L, Czerniawska-Mysik G, Adamek-Guzik T. Influence of tobacco dust on the respiratory system and selected immunological parameters. *Przegl Lek* 2002;59(10):789–792.
17. Sünter AT, Bağırıcı F, Dündar C, Marangoz A, Pekşen Y. Lung functions in workers exposed to tobacco dust. *Türk J Med Sci* 2001;31(2):143–146.
18. Huuskonen MS, Järvisalo J, Koskinen H, Kivistö H. Serum angiotensin-converting enzyme and lysosomal enzymes in tobacco workers. *Chest* 1986;89(2):224–228.
19. Osim EE, Musabayane CT, Mufunda J. Lung function of Zimbabwean farm workers exposed to flue curing and stacking of tobacco leaves. *S Afr Med J* 1998;88(9):1127–1131.
20. Kearney GD, Chatterjee AB, Talton J, Chen H, et al. The association of respiratory symptoms and indoor housing conditions among migrant farmworkers in Eastern North Carolina. *J Agromedicine* 2014;19(4):395–405.
21. Mirabelli MC, Hoppin JA, Chatterjee AB, Isom S, et al. Job activities and respiratory symptoms among farmworkers in North Carolina. *Arch Env Occup Heal* 2011;66(3):178–182.
22. Wendling JM, Oster JP, De Blay F, Pauli G. Toux spasmodique par sensibilisation à la feuille de tabac chez une agricultrice A propos d'un cas. *Rev Fr Allergol Immunol Clin* 1994;34(6):498–500.
23. Khomenko AG, Ozerova L V. Occupation exogenous allergic alveolitis. *Probl Tuberk* 1996;(6):72–75.
24. Khomenko AG, Zhalolov Z, Dmitrieva LI. Clinical variants of the course and the characteristics of the x-ray changes in extrinsic allergic alveolitis--tobacco growers' disease. *Ter Arkh* 1990;62(3):117–121.
25. Chomenko AG, Dmitrieva LI, Zhalolov Z. The tobacco grower's lung: x-ray variants. *Radiol Diagn (Berl)* 1990;31(5):513–520.
26. Nefedov VB, Popova LA, Zhalolov ZZ. Lung function in tobacco growers suffering from exogenous allergic alveolitis. *Ter Arkh* 1991;63(3):124–126.
27. Ghosh SK, Parikh JR, Gokani VN, Rao MN, et al. Studies on occupational health problems in agricultural tobacco workers. *J Soc Occup Med* 1980;30(3):113–117.
28. Cargnin MC dos S, Teixeira C de C, Mantovani VM, Lucena A de F, Echer IC. Cultura do tabaco versus saúde dos fumicultores. *Texto Context enferm* 2016;25(2):e2940014.
29. Yoshioka D, Ishii H, Hatano Y, Umeki K, et al. A case of Eosinophilic Pneumonia in a tobacco harvester. *Allergol Int* 2011;60(4):551–554.
30. Fiori NS, Fassa AG, Faria NM, Meucci RD, et al. Wheezing in tobacco farm workers in Southern Brazil. *Am J Ind Med* 2015;58(11):1217–1228.
31. Van Minh H, Giang KB, Bich NN, Huong NT. Tobacco farming in rural Vietnam: questionable economic gain but evident health risks. *BMC Public Health* 2009;9(1):24.
32. Ignacak A, Guzik T, Sliwa T, Scibor M, Sanokowska E, Czerniawska-Mysik G, et al. The effect of chronic exposure to tobacco dust on nasal mucosa. *Allerg Astma Immun.* 2001;6(3):149–154.
33. Haber H, Raber W, Vetter N. Bronchial asthmatic disease associated with tobacco dust—an occupational lung disease?. *Wien Klin Wochenschr* 2004;116 Suppl 1:38–39.
34. Schachter EN, Zuskin E, Goswami S, Castranova V, et al. Pharmacologic effects of tobacco dust extract on isolated Guinea pig trachea. *Chest* 2003;123(3):862–868.
35. Schachter EN, Zuskin E, Gadgil A, Rienzi N, Goswami S. Hyperresponsiveness to tobacco dust extract in sensitized guinea pig trachea. *Pulm Pharmacol Ther* 2004;17(2):65–71.
36. Huuskonen MS, Husman K, Järvisalo J, Korhonen O, et al. Extrinsic allergic alveolitis in the tobacco industry. *Br J Ind Med* 1984;41(1):77–83.
37. Antó JM, Sunyer J, Basagaña X, Garcia-Esteban R, et al. Risk factors of new-onset asthma in adults: a population-based international cohort study. *Allergy* 2010;65(8):1021–1030.
38. James AL, Knuiman MW, Divitini ML, Hui J, et al. Risk factors for respiratory symptoms in adults: The Busselton Health Study. *Respirology* 2013;18(8):1256–1260.
39. Chiba Y, Murata M, Ushikubo H, Yoshikawa Y, et al. Effect of cigarette smoke exposure *in vivo* on bronchial smooth muscle contractility *in vitro* in rats. *Am J Respir Cell Mol Biol* 2005;33(6):574–581.
40. Hong JL, Lee LY. Cigarette smoke-induced bronchoconstriction: causative agents and role of thromboxane receptors. *J Appl Physiol* 1996;81(5):2053–2059.
41. Hong JL, Rodger IW, Lee LY. Cigarette smoke-induced bronchoconstriction: cholinergic mechanisms, tachykinins, and cyclooxygenase products. *J Appl Physiol* 1995;78(6):2260–2266.
42. Matsumoto K, Aizawa H, Inoue H, Takata S, et al. Role of thromboxane-A2 and cholinergic mechanisms in bronchoconstriction induced by cigarette smoke in guinea-pigs. *Eur Respir J* 1996;9(12):2468–2473.
43. De Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: is it really different? *Eur Respir Rev* 2013;22(127):44–52.
44. Chongo-Faruk V. Skin exposure, symptoms and asthma in occupational settings – is there a link? *Curr Allergy Clin Immunol* 2017;30(4):251–257.