# Risks to respiratory health in the grain industry

Prepared by the Health and Safety Executive

A detailed literature search was carried out to summarise evidence about respiratory disease caused by exposure to grain dust. Long term epidemiological studies examining the risk for respiratory disease in grain workers were undertaken in Canada and the USA from the 1970s to the late 1990s. Smaller studies were undertaken in the UK and Europe but mostly focussed on respiratory disease in arable and livestock farmers.

The conclusion of this review is that the damaging effects of grain dust on the respiratory tract are accumulative and occur at high concentrations of exposure. Acute responses also occur and include declines in lung function as well as irritation and inflammation of the airways. There is less evidence that grain dust exposure causes occupational asthma despite the dusts containing allergens. This may be due to a 'healthy worker' effect with those already having, or developing, asthma leaving employment earlier than others. There is stronger evidence that the long term effects of exposure include emphysema, chronic obstructive pulmonary disease and interstitial fibrosis of the lung. The risk of developing extrinsic allergic alveolitis has reduced through preventing damp conditions in stored grain.

**HSE Books**

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| American Conference of Industrial Hygienists | ACGIH |
| Body mass index | BMI |
| Confidence interval | CI |
| Chronic obstructive pulmonary disease | COPD |
| Control of substances hazardous to health | COSHH |
| Diffusion lung capacity for carbon monoxide | DLCO |
| Extrinsic allergic alveolitis | EAA |
| Endotoxin units | EU |
| Forced expiratory volume in one second | $FEV_1$ |
| Forced expiratory flow | FEF |
| Formyl-met-leu-phe peptide | FMLP |
| Forced volume vital capacity | FVC |
| Health & Safety Executive | HSE |
| Immunoglobulin G | IgG |
| Immunoglobulin E | IgE |
| Interleukin 1 | IL-1 |
| Interleukin 6 | IL-6 |
| Interleukin 8 | IL-8 |
| Lipopolysaccharide | LPS |
| Maximum exposure limit | MEL |
| National Institute for Occupational Safety and Health | NIOSH |
| Organic toxic dust syndrome | OTDS |
| Occupational Safety and Health Administration | OSHA |
| Permissible exposure limit | PEL |
| Personal protective equipment | PPE |
| Standardise mortality ratio | SMR |
| Transforming growth factor | TGF |
| Threshold limit value | TLV |
| Tumour necrosis factor | TNF |
| Workplace exposure limit | WEL |

# CONTENTS

# KEY MESSAGES

- Grain dust from wheat, oats, barley, rye, and corn contains plant proteins and chemicals, soil particles, microorganisms and their toxins, small invertebrates, and low levels of farming chemicals. Some of these constituents have the potential to cause asthma, and microbial toxins to cause inflammation in the lung.

- Occupational exposure to grain dust is considered a risk for lung disease.

- To assess the strength of evidence that grain dust causes lung disease a review of published research was carried out on studies from the 1970s to 2012.

- Long term studies in cohorts of grain workers from Canada and the Unites States concluded that their lung function declined over many years of exposure and more than in workers not-exposed to grain dust.

- Studies from the UK and Europe mostly focussed on general farming activities and were less useful in helping to discriminate the effects of grain dust on lung disease.

- Acute effects of grain dust include rapid but reversible declines in lung capacity with irritation and inflammation in the airways causing coughing, chestiness and breathlessness.

- The main conclusion of this review is that the effects of grain dust on the lung are accumulative and occur at high dust concentrations. Over many decades of exposure this may cause thickening of the airways, and chronic obstructive pulmonary disease in some individuals.

- There is limited evidence for excess asthma cases in grain workers, despite these dusts containing allergens. A 'healthy worker' effect with employees suffering from asthma and other respiratory allergies leaving employment in this industry at an early stage of their career may explain this.

- Cigarette smoking is likely to accelerate the decline in lung function in those exposed to grain dust.

# EXECUTIVE SUMMARY

A detailed literature search was carried out to summarise evidence about respiratory disease caused by exposure to grain dust. Large epidemiological studies were undertaken in Canada and the USA (including longitudinal studies) for over 30 years from the late 1970s. In contrast, fewer studies were undertaken in the UK and Europe and these focussed more on respiratory disease amongst farmers (including grain farmers).

The overall conclusions of this review are that the most damaging effects of grain dust on the respiratory tract are accumulative and occur at high concentrations. Acute responses occur and include declines in ventilatory capacity of the airways, and irritation and inflammation of the airway lining. Long term exposure to grain dusts may cause chronic obstructive pulmonary disease, allergic airway disease, and an impairment of lung function.

There is limited evidence for excess asthma cases amongst workers exposed to grain dust despite these dusts containing allergens. The lack of reported asthma cases may be due to a 'healthy worker' effect as studies have shown that staff with pre-existing allergy, or those at greater risk of developing allergy, typically leave the industry soon after starting employment. There is evidence of a risk of extrinsic allergic alveolitis (EAA) a delayed respiratory allergy but mostly in those exposed to damp and mouldy grain.

Workers exposed to high airborne levels of grain dust develop acute and chronic respiratory symptoms, which include cough, phlegm, wheezing and dyspnoea and indications of obstructive airway disease. These responses occur in the upper and lower airways and are attributed to grain dust and microbial contaminants in the dust. Grain dust provokes inflammation and mucous congestion in the airways and chronic inflammation may reduce efficient gas exchange by causing the connective tissue surrounding the airways to thicken.

Grain workers suffer reductions to their lung capacity irrespective of whether they are predisposed to develop allergy. Smoking is also a contributory risk factor for the development of inflammatory disease in the airways. Smokers and those inhaling grain dust experience similar reductions in lung capacity but in grain workers that also smoke some will suffer greater reductions in lung function.

When grain dust is inhaled it causes an acute reaction which results in airway obstruction. This reaction does not seem to be only related to respiratory allergy but is caused by physiological and inflammatory reactions to the dust. Bacterial toxins (e.g., endotoxin), may be a key factor provoking inflammatory reactions but other microbial toxins and constituents of grain dust are also implicated.

If workers are occasionally exposed to high levels of grain dust, evidence suggests the decline in their lung function may recover later (e.g., for seasonal farm workers involved in grain harvesting). Longitudinal studies of grain workers chronically exposed show that not only does the prevalence of cough and phlegm increase but during the first years of work the rate of decline in lung capacity is accelerated compared to non-exposed 'non-smoking' workers of equivalent age. This rate of decline appears to slow in later years of service but the eventual outcome is impaired ventilatory capacity. Those retiring after working in the industry for decades are at increased risk of developing chronic respiratory disease if they have been exposed to high concentrations of airborne grain dust. Some studies suggest that exposure above 4mg/m$^3$ 8Hr TWA is sufficient to cause this damage.

# 1.0 INTRODUCTION

*1.1 Aim:*

To summarise evidence of respiratory ill-health effects associated with exposure to grain dust

*1.2 Objectives*
- To undertake a review of published studies concerning occupational respiratory disease attributable to exposure to grain dust
- To assess the relationship between exposure to grain dust and the severity of respiratory disease

*1.3 Background:*

Information was collected about the Grain industry and from published studies that examined risks for respiratory ill health caused by exposure to grain dust. This evidence was summarised using Mindjet Manager Pro software and a review of the evidence prepared. The first part of the review summarises the evidence for each type of respiratory disease. The annex contains a more detailed technical summary about the different hazardous constituents in grain dusts.

In the United States more than 5 million individuals were involved in agricultural production in the late 1970s when large-scale investigations of this problem began. At the same time in Canada, the size of the workforce was estimated as ~170,000 with approximately 125,000 involved in the agricultural production of grains and ~35,000 involved in the transport and milling of grain. At present it is not clear in the UK how many people work across the range of businesses involved in the production, transport and processing of grains (see Table 1 for summary).

In 2009, it was estimated that in the UK approximately 1.9 million hectares of wheat were grown on approximately 45% of the arable land for use in bread, biscuit making, and animal feeds. Once harvested, grains are usually purchased by merchants, placed in central stores and then transported to mills or other processing units (e.g., the animal feed industry). In 2008 to 2009, wheat produced in the UK accounted for 80% of that used by millers and the remaining was imported. In GB there are ~30 milling companies running fifty-nine mills milling a total of 5.7 million tonnes of wheat each year (NABIM: UK Flour Milling Industry 2009).

**Table 1:** List of key activities / scenarios where exposures to grain dust occurs**:**

| Process or task | Grain industry sector or other industry |
|---|---|
| Harvesting | Farming |
| Grain cleaning | Grain merchant, flour milling, maltings, malt milling |
| Grain drying | Farming, grain merchants, flour milling |
| Storage and distribution | Farming, grain merchant, flour milling, maltings, malt milling, road hauliers, stevedores |
| Grain silo cleaning | Farming, grain merchant, flour milling, maltings, |
| Milling/grinding | Flour milling, malt milling, distilleries, |
| Animal feed production | Feed milling |
| Mixing | Grain merchant, flour milling, feed milling, malt milling |
| Transferring and storing grain at terminals and docks (imports) | Stevedores (loading and unloading of ships containing) flour |

*Table taken from Spankie S and Cherrie JW: HSE Research Report (2010) RR829

Dusts are generated as a result of energetic processes from the production, harvest, transfer, storage, and processing of grain. The size range of the particles in this dust ranges from ultrafine (<0.1μm diameter) to fine sized particles in the respirable (<5μm diameter) and non-respirable range (>5μm

diameter); it has been estimated that up to 40% of the particles have the potential to penetrate to the gas exchange surfaces of the lung (Kirkhorn and Garry 2000).

Grain dust is ~60-75% organic material and ~25-40% inorganic material (Yoshida and Maybank 1980). The organic components include fragments of grains (e.g., wheat, oats, barley, rye, and corn); oil seeds (e.g., rapeseed, linseed, and sunflower seed); and pulses (the edible seeds of legumes such as peas and soybeans) (Becklake: 1980b). The dust also contains the decomposition products of grains, seeds, and pulses (Chan-Yeung and Ashley: 1978); inorganic materials such as soil and traces of chemicals (Yoshida and Maybank: 1980); microorganisms (NIOSH: 1986); insects, insect parts, and mites; hairs, feathers, and excreta of rodents and birds (Becklake: 1980b); fragments of plant matter (Becklake: 1980b); fertilizers, pesticides, and herbicides (Federal Register: 1980).

In Great Britain, grain dust is a hazardous substance under the Control of Substances Hazardous to Health Regulations 2002 (as amended) with a workplace exposure limit (WEL) of 10 mg/m$^3$ for an 8hr time weighted average (TWA). Comprehensive details of the hazardous constituents of grain dust are provided in Appendix 1. The US Occupational Health & Safety Administration (OSHA) permissible exposure level (PEL) is also 10 mg/m$^3$ for grain dusts (oats, wheat, and barley) and 5 mg/m$^3$ for respirable dust (NIOSH 1997). The American Government Council of Industrial Hygienists (ACGIH) recommended a lower threshold limit value (TLV) for grain dust from wheat, oats and barley of 4mg/mg$^{-3}$ (ACGIH: 2000). This was based on evidence that respiratory symptoms were observed in grain workers exposed to approximately10 mg/m$^3$ but were diminished below 4mg/m$^3$. However, due to the difficulty of defining a threshold adverse effect level and for the industry to control exposures below 4mg/mg$^{-3}$, OSHA decided to retain the PEL of 10 mg/m$^3$ 8hr TWA for grain dust. The Health Council of the Netherlands Committee has set out evidence for a health-based recommended occupational exposure limit (HBROEL) for inhalable grain dust of 1.5 mg/m3 as 8-hour time-weighted average (Health Council of the Netherlands. Grain dust: 2011). Contemporary evidence about exposure to grain dust in different parts of UK industry has recently been examined and summarised by Spankie and Cherrie (2010). This survey showed that during the 1990's average grain dust levels were above 5mg/m$^3$ (with highest exposures for work at grain terminals and during grain drying) but in recent time the average levels have reduced to ~3mg/ m$^3$ (5-20% of personal exposures being greater than 10mg/m$^3$).

# 2.0 METHODOLGY

*2.1 Literature review:*

The appropriate search terms were identified in consultation with the HSE information service team. These terms were divided into two groups (see Table 2), and searches carried out combining a term in list one with one in list two. The searches were based upon proximity of the terms irrespective of their order within the document but they had to be no more than five words apart.

**Table 2:** Summary of search terms

| List 1 | List 2 |
|---|---|
| Asthma | Grain (near dust) |
| Bronchitis | Wheat (near dust) |
| Breathing difficulties | Rye (near dust) |
| Extrinsic (near) allergic (near) alveolitis | Barley (near dust) |
| Irritant (near) respiratory | Oats (near dust) |
| Reversible airway obstruction | Maize (near dust) |
| Respiratory (near) disease | |
| Occupation (al)(near exposure) | |
| Health | |
| Epidemiological | |
| Exposure (near measurement) | |

The HSE library services completed the search on OSHROM (HSELINE, NIOSHTIC, CISDOC, RILOSH and OSHLINE) databases, Embase, Medline, Healthsafe and Web of Science (Table 2), between 1960 and February 2009. Additional searches were carried out using PubMed, Web of Science, and ToxNet covering the period from 1980 to December 2012. This period of search was chosen to reflect the earliest large cohort studies of ill health in the US and Canadian grain industry from the early 1970s onwards

A total of 617 references were added to an Endnote reference database and the titles and abstracts reviewed by the team. Relevant abstracts were identified and sifted on the basis of the specific links between these topics. The published studies were selected on the basis of the priority topics listed in Table 3, items 1-3 of this list being the most important topics. Following this sift a total of 170 relevant papers were short listed and saved into a second Endnote reference database.

**Table 3:** Summary of key topics and priority attached to each topic (from most to least 1-10)

| Topic of reference | Priority |
|---|---|
| Grain dust (including types of grain) & occupational respiratory disease | 1 |
| Epidemiological study (retrospective, cross sectional, longitudinal) | 2 |
| Clinical investigations | 3 |
| Personal exposure to grain dust (hygiene investigations) | 4 |
| Interventional studies | 5 |
| Case studies | 6 |
| Experimental respiratory challenge studies (human) | 7 |

Priority was given to studies of respiratory disease in those occupationally exposed to grain dust, with emphasis on retrospective, cross-sectional, or prospective studies involving large working populations. Review papers were included and clinical investigations of respiratory symptoms caused by inhalation of grain dust. Studies of respiratory symptoms were preferred over studies that only dealt with exposure to grain dust. Some experimental investigations into the mechanisms by which grain dust

causes respiratory symptoms were included but biased toward human inhalation studies or studies on human cells. Experimental whole animal and animal cell cultures studies were given a lower priority.

The different topics covered by these papers are summarised in the HSE Grain Industry MindJet Map. The number of published studies about respiratory disease in those exposed to grain dust is summarised by year of publication in Figure 1.

**Figure 1:** Number of papers published each year from 1960 to 2012 that specifically investigated the effects of occupational grain dust exposure on respiratory health. This list is not comprehensive but includes most studies published in English and in the countries such as the US, Canada, and Europe.
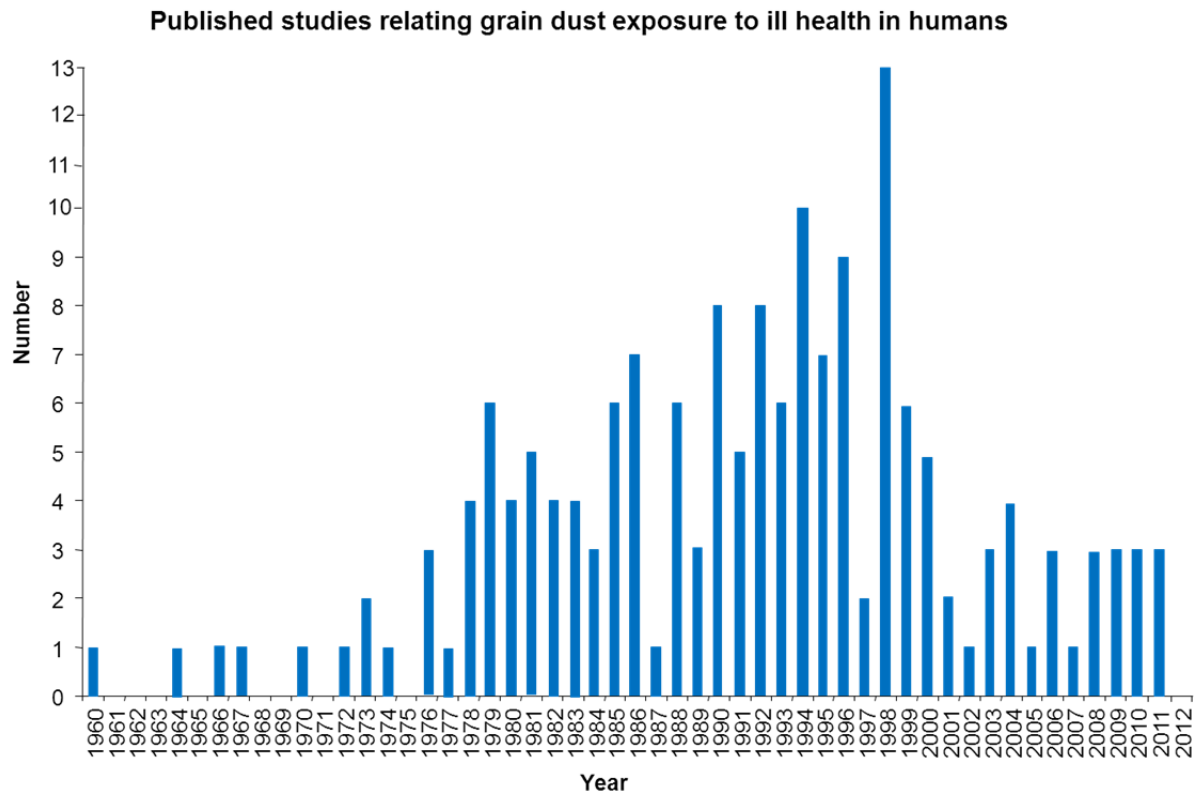


The search identified many published studies describing respiratory symptoms in workers occupationally exposed to grain dust including case reports, cross sectional and longitudinal epidemiological studies, and studies investigating the impact of reducing grain dust exposure on subsequent levels of respiratory disease. Cohort studies of apprentices and of those leaving the industry were also reported. The largest proportion of clinical studies investigated serial declines in lung capacity as acute and chronic responses to inhaled grain dust. Very few papers specifically reported the occurrence of chronic obstructive pulmonary disease but this might have reflected the publication of these studies before 2000. A small number of studies reported on the occurrence of sensitisation (production of allergen specific antibodies) to grain and constituents of grain dust typically species such as mites or fungi. More studies were published on the irritant and inflammatory effects of grain dust in the airways and on the pro-inflammatory role of bacterial toxins. A number of these studies examined specific risk co-factors for respiratory disease such as smoking.

The majority of the epidemiological and medical studies were conducted in Canada and the USA and included large epidemiological surveys of the industry (grain producers, transport and storage workers, millers), and detailed clinical investigations including inhalation challenge studies. Most of these epidemiological studies were cross sectional in design (DoPico *et al*: 1977; Broder *et al*, 1979;

Becklake *et al*: 1980a; Chan-Yeung *et al*: 1980; Dosman *et al*: 1980; Herbert *et al*: 1981; Cotton *et al*: 1983; Yach *et al*: 1985; Heller *et al*: 1986). A large twelve year longitudinal study was also undertaken which examined the rate of decline in lung capacity in grain elevator worker pre and post an intervention to reduce the average level of exposure to grain dust (Pahwa *et al*: 2008).

There were fewer and smaller European studies specifically addressing exposure and health effects amongst grain workers (Table 5a-h in Appendix 2) with the exception of exposure assessment studies carried out by HSE and by European researchers (Peelen, *et al* 1996; Eduward *et al* 2001; Halstensen *et al*: 2007; Swan *et al*: 2007; Spankie and Cherrie 2010; Wijnand *et al*: 2012). A number of smaller studies had been undertaken across the EU looking at respiratory health amongst farm workers including activities related to harvesting of grain (Patel *et al*: 1981: Heller *et al*: 1986; Blainey *et al:* 1989; Smid *et al*: 1992: Gimenez C *et al*: 1995; Massin *et al*: 1995; Peelen *et al:* 1996; Post *et al*: 1998; Holland Skorska *et al*: 1998; Godnic-Cvar *et al*: 1999; Baser et al: 2003)

From 2000 onwards fewer epidemiological investigations amongst grain workers in Canada and the US were published but research groups continued to publish analysis of the results from the large longitudinal studies started during the 1990s. Other studies published between 2000 and 2012 focussed on sensitisation to contaminants in grain dust (e.g., insects and mites) (Halstensen *et al*: 2007; Gora *et al*: 2009) and exposure to fungal and bacterial toxins in grain (Basinas *et al*: 2011].

# 3.0 RESPIRATORY DISEASE IN GRAIN WORKERS

The prevalence of respiratory symptoms for different types of grain workers and in different countries is summarised in Tables 5a-5h in Appendix 2. The information presented in these tables on symptom prevalence should be interpreted with caution. The design of many of these studies differed and the extent to which the lung function and symptom prevalence were determined also differed. Where possible the data reporting the changes in symptom prevalence or lung function have been expressed as a percentage difference from control non-exposed groups.

This summary of respiratory symptoms associated with exposure to grain dust could have presented the findings on the basis of the speed of onset and severity of symptoms (in which case asthma can be regarded as a rapid airway response). However, the results can also be presented in terms of the aetiology of the disease (as it is currently understood), separating those symptoms which can occur within a short time after exposure to grain, and the types of respiratory disease which has a long latency (taking month to years to develop). Another dimension is the impact of the hazard potency of individual grain constituents. Some constituents of dusts (e.g., mineral dusts and plant fibres) can irritate the airways and may do so within minutes to hours, if exposure is sufficiently high. Rapid inflammatory responses to microbial toxins can also occur within hours if the exposures are very high. In contrast, airborne allergens which can cause new cases of respiratory allergy are effective at very low concentrations (e.g., below $0.001 \text{mg} / \text{m}^3$) and associated with exposures over months and years). For chronic obstructive pulmonary disease exposures over years and decades may be required.

In this review the results have been organised in terms of the understood aetiology of the symptoms and disease (see Figure 1 for a summary) separating those exposures capable of causing acute changes from those associated with 'chronic' exposures and delayed changes in the respiratory tract.

## 3.1 Acute and Short Term Effects of Grain Dust on the Respiratory Tract

Due to the combination of inorganic and organic constituents of grain dust acute effects in the respiratory system may vary considerably, with the potential for irritation, inflammation, and toxicity. Irritant substances cause inflammation in the airways by stimulating nerves endings or by triggering innate immunity. Innate immune responses can stimulate airway mucous secretion and an influx from the blood supply of immune cells involved in inflammation and infection control. Innate immune responses are usually triggered by bacterial or viral infections but non-specific agents can also provoke this response. When continuously activated, inflammation can progressively damage the airways and gas exchange surfaces of the lung.

Acute effects of grain dust on the respiratory tract include bronchial reactivity, bronchitis, and for dust with high endotoxin content organic dust toxic syndrome (ODTS). Apart from ODTS the prevalence of acute symptoms is higher for workers performing tasks where grain dust levels are high ($>10 \text{mg/m}^3$) but for ODTS additional factors such as heavy mould contamination is a pre-requisite. Reversible reductions in lung vital capacity occur acutely (within hours) following inhalation of grain dust and other rapid changes include inflammation in the airways promoting fluid and mucous secretion.

3.1.1 Non-allergic Airflow Obstruction

A symptom commonly reported in many early studies of grain dust has been termed 'asthma-like' bronchial reactivity (doPico et al: 1982; Broder et al: 1984; McCarthy et al: 1985; Enarson et al: 1985; James et al: 1986; James et al: 1990; Vedal et al: 1988; Huy et al: 1991; Zejda et al: 1992; Pahwa et al: 1994; Pahwa et al: 2003; Pahwa et al: 2008; Tielemans et al: 1994; Post W et al: 1998). This was characterised as a reversible airway reaction to inhaled grain dust but differed from allergic asthma since it occurred in workers with no prior history of allergy. The symptoms included chest tightness, shortness of breath (dyspnoea), and cough, and were typically mild and self-limiting. It was noticed that in those affected, ventilatory capacity of the lung declined across the working shift (e.g. using spirometry forced expiratory volume (FEV1) was found to decline but usually by less than 10%.

However, this short-term decline predicted those who were likely to develop a progressive decline in lung function (Schenker *et al*: 1998) and the severity of the response was shown to be exposure dose dependent (Chan-Yeung *et al*: 1979). This has subsequently been referred to by others as 'asthma-like' syndrome a non-allergic airflow obstruction (Chan-Yeung *et al*: 2006). It is characterised by a cross shift decline in lung function that may or may not be associated with other symptoms (such as cough, sputum production, wheeze, or chest tightness). To avoid confusion with current terminology this will be referred to from this point as grain induced airflow obstruction.

Such short-term reductions in ventilatory capacity of the airways across a working shift, or a working week, have consistently been reported (Chan-Yeung *et al*: 1981; Tabona *et al*: 1984; James *et al*: 1986) and were directly related to high ambient concentrations of grain dust (doPico *et al*: 1983, Corey *et al*: 1982).

In one study as many as 50% of grain workers experienced a cross-shift decline in FEV1. When sixteen cross-sectional studies of grain workers (from 1941– 1986) were reviewed declines in FEV1 and forced vital capacity (FVC) were typically observed for the exposed compared to non-exposed controls. The prevalence rates for wheeze, cough, phlegm, and shortness of breath also were higher in these workers (Chan-Yeung *et al*: 1992b).

In a more recent cross sectional study, Reynolds *et al* (2012) reported data on personal exposure to inhalable airborne dust and endotoxin quantified over one work shift in 53 grain elevator workers (as well as groups of farmers exposed to other organic dusts). Cross shift changes in lung function parameters were measured and the impact of exposure took into account modifying factors such as smoking, use of pesticides and herbicides, obesity, age, ethnicity, previous allergy and genetic variation influencing susceptibility to endotoxin. The authors concluded that amongst grain workers acute cross shift declines in lung function were associated with exposure to endotoxin (measured as 3-OH fatty acid residues). Greater exposure associated reductions in lung function were seen amongst current smokers than non-smokers and amongst those using pesticides or herbicides.

The severity of these acute respiratory reactions and cross-shift declines in lung function has been shown to reduce several weeks after continued exposure to grain dust. This is consistent with a physiological adaptation of the airways to the irritant effects of grain dust, and this differs from the progression of symptoms that occurs in asthma sufferers. For example, forty-one seasonal grain handlers and ten public works department employees (non-exposed controls) were studied during their first few weeks in work. FEV1 decreased by a mean of 321ml over the first three weeks of work in the grain workers before returning to the levels seen in non-exposed subjects. The frequency of these symptoms and the decreases in FEV1 were greater in grain handlers exposed to dust >20 mg/m$^3$ compared to workers exposed to <10 mg m$^3$ (James *et al*: 1990). Those with allergic asthma typically develop persistent airway hyper responsiveness and may react progressively to smaller concentrations of allergen. In contrast airflow obstruction in grain workers typically occurs only in those exposed to high concentrations of the dust (Schenker *et al*: 1998).

It has been noted that grain dust can activate innate immune reactions (Olenchock *et al*: 1980); stimulate the release of histamine (Park *et al*: 1999); and the influx of cytotoxic immune cells into the airways (Von Essen *et al*: 1988). Phagocytic immune cells such as the neutrophil are the predominant cells found within the airways and these cells release mediators and cytotoxic products that cause inflammation of the airways. No specific agents in grain dust have been specifically identified as causing this airway response. However, in volunteers challenged with grain dust depleted of bacterial endotoxin, declines in FEV1 still occurred (Clapp *et al*: 1993; Post *et al*: 1998) suggesting that endotoxin alone was not responsible for the decline. In addition to these acute effects of grain dust many studies of workers chronically exposed to grain have reported persistent declines in lung capacity.

3.1.2 Organic Dust Toxic Syndrome

This acute response occurs when grain dust containing high bacterial and fungal content are inhaled. The symptoms include fever, chills, headaches, and shortness of breath with chest tightness and airflow obstruction. Subjects typically experience burning sensations in the throat and trachea and a build-up of mucus in the airways resulting in a reversible obstruction of airflow. The symptoms are caused by an

acute inflammatory response which has systemic involvement and is not restricted to the respiratory tract. Symptoms such as raised body temperature typically peak 4–8 hrs after exposure and subside once exposure is discontinued (Schenker *et al*: 1998).

The reported prevalence of ODTS amongst grain workers varies from a few percentages to 25% in different studies (Kleinfeld *et al*: 1968; Tse *et al*: 1973; doPico *et al:* 1977, Chan-Yeung *et al*: 1980; Cockroft *et al*: 1983; Manfreda *et al* 1986; Broder *et al*: 1979). A prevalence (ever experienced) of fever in 10–15% of farmers has been reported (Malmberg *et al*: 1985; Malmberg *et al*: 1988; Husman *et al*: 1990).

In an analysis of four large epidemiological studies of respiratory sensitisation and symptoms in occupations exposed to endotoxin (including 2010 agricultural workers), Basinas *et al* (2011) reported that current endotoxin exposure was associated with a dose related reduction in the prevalence of allergic sensitisation, atopy, and hay fever, but an increase in the risk for ODTS occurred above exposure levels in excess of 100 EU/m$^3$.

Endotoxin is one of the main microbial agents causing ODTS (Chan-Yeung *et al*: 1985) but other bacterial and fungal toxins can also provoke this reaction (Abel and Czop: 1992; Houba *et al*: 1992; Massion *et al*: 1994; Kumar *et al*: 1993; Peetermans *et al:* 1994; Johnson *et al:* 1992). In challenge studies, the inhalation of ~100μg of endotoxin causes general fever and inflammation of the airways and alveoli (Rylander *et al*: 1989; Sandström *et al:* 1992; Martich *et al*: 1993) within hours of exposure. Endotoxin levels as low as 5μg in the inhalable fraction of dust from swine confinement buildings cause symptoms of ODTS (Malmberg *et al*: 1993; Zhiping *et al*: 1996). However, grain dust depleted of endotoxin still causes inflammation in the airways but to a lesser extent [Von Essen *et al*: 1994**).** Reynolds *et al* (2012) demonstrated that acute declines in lung function were associated more strongly with 3-OH fatty acid residues of endotoxin and occurred more steeply in those recently employed in handling grain as well as individuals with genetic variability in the Toll like receptor-4 (this is an endotoxin receptor that triggers its pro-inflammatory effects).

Fungal mycotoxins may also cause ODTS (Land *et al*: 1987, Rask-Andersen *et al:* 1990). Alveolar lavage fluid taken from patients with ODTS contained large numbers of fungal spores (e.g., from *Aspergillus sps*, *Penicillium sps*) (Karlsson *et al*: 1989; Malmberg *et al*: 1993) and it was estimated that as many as $2.3 \times 10^{10}$ spores may be required to provoke ODTS. In one reported case study, 82% of college students attending a party where damp straw had been placed on the floor developed myalgia, cough, and low-grade fever within several hours (Brinton: 1987). It has also been reported that non-mouldy grain may provoke symptoms in those working in grain silos exposed to high levels of dust (doPico *et al*: 1982b; Cockroft *et al*: 1983).

In farmers challenged with mouldy dust, the lung gas diffusion capacity for carbon monoxide (DLCO) was reduced by 26% of the predicted level compared to only 15% for control healthy subjects. The body temperature of the farmers also increased by +1.3$^0$C compared to 0.7$^0$C in the healthy referents (Vogelmeier *et al*: 1993). This suggested the presence of mould sensitivity amongst the farmers. This observation is at odds with other studies showing that early childhood exposure to high concentrations of endotoxin on farms can lead to greater tolerance and may reduce risks for development of atopy and allergic disease (Elholm *et al*: 2010).

3.1.3 Rhinitis and conjunctivitis

The prevalence of nasal and ocular symptoms is often high in work environments that are dusty. Rhinitis and conjunctivitis can be caused by the irritant effects of dusts but also occur as allergic responses to allergens present in organic dusts such as grain and flour. Irritants in grain dust may consist of biological materials (e.g., fragments of the husk) but also inert constituents such as particles of soil (see Annex sections 4.1.5 and 4.1.6). It is likely that irritant materials cause common responses

in most people due to their mode of action (e.g., their directly irritant and toxic properties), however the risk for developing allergic responses is dependent on factors such as a family history of atopy (atopy is a predisposition towards developing allergy to common environmental allergens such as pollen, house dust mite etc.). In many of the studies of exposure to grain dust the prevalence of ocular and nasal symptoms is high but it is not clear whether these symptoms are mostly related to irritant or to allergic responses (see summary tables 5a, b, d, f, g, h).

A study in Finland reported that 20% of rhinitis cases in farmers were occupationally related and caused by flour, wood, animal, and vegetable dusts (Kanerva and Vaheri: 1993; Schenker *et al*: 1998). Amongst workers exposed regularly to grain dust, nasal irritation, nasal congestion, and runny nose are common (Darke *et al*: 1976; Manfreda *et al*: 1986; Hurst and Dosman: 1990; Clap *et al*: 1993) and symptoms occur more frequently amongst younger staff exposed to high levels of dust

In a survey of 300 grain elevator workers exposed to grain dust 77% complained of eye symptoms, 64% of nasal symptoms, and 88% of one or more respiratory symptoms that were independent of age and duration of employment (doPico *et al*: 1977). DoPico *et al* (1983) noted in grain elevator workers exposed to an average dust level of 3.3 mg / m$^3$ that the prevalence of nasal symptoms was 38% in the exposed vs 26% in the non-exposed workers. In another study of one hundred male grain mill workers in Sudan, the prevalence of chronic rhinitis and sinusitis was 17% compared to 3% in the non-exposed control group; and the prevalence of conjunctivitis was 19% compared to 3% in the controls. Age, height, and smoking prevalence were not significantly different between the two groups, and the symptoms were attributed to inhalation of grain and flour dust (Awad *et al*: 1981). Given that flour dust is likely to contain a greater content of allergen, the higher prevalence of ocular and upper airway symptoms may have been driven more by the flour exposure. Dockworkers handling grain have also been reported to have an approximately seven fold higher risk of developing nasal symptoms, and an eightfold higher risk of developing chronic phlegm compared to civic workers and 'non-exposed' controls (Dimich-Ward *et al*: 1995).

The occurrence of nasal and ocular symptoms also increases in a dose dependent way with a 10.3% prevalence reported for the lowest exposures (mean dust of ~0.5mg/m$^3$) compared to 36.4% prevalence at the highest exposure levels (mean dust of ~17.6mg/m$^3$) (Bachmann and Myers: 1991).

In a health surveillance study of male grain food manufacturing workers the prevalence of cough, breathlessness, wheeze, and chest tightness ranged between 8-13% and for rhinitis approximately 20%. Specific occupational activities associated with this increased risk of rhinitis were examined but smoking was not a significant risk factor; younger workers were more likely to report rhinitis; and rhinitis was not related to a reduced ventilatory capacity (Deacon and Paddle: 1998). Further evidence that younger employees were more at risk of these symptoms came from a study in which employees were examined at the start of their employment and two and a half months later. In the newly employed group the prevalence of respiratory congestion and ocular irritation increased compared to employees working in the grain industry for more than nine years. The lowest prevalence of symptoms occurred amongst the 'non-exposed' control group (Broder *et al*: 1984).

The pro-inflammatory effects of grain on the nasal passage do not seem to depend on a history of allergic rhinitis, atopy, or previous exposure to grain dust (Clapp *et al*: 1994; Becker *et al*: 1999). When volunteers inhaled grain dusts both non-atopic grain workers and workers who were not prior exposed to grain dust, had similar inflammatory markers in their nasal fluid. This inflammatory effect may also be related to bacterial toxins (such as endotoxin) stimulating mucous secretion in the airways (Blaski *et al*: 1996).

3.1.4 Asthma

Asthma is an example of an immediate hypersensitivity (allergic responses typically occur rapidly within minutes to hours after exposure to allergens) and as a chronic condition can remodel the conducting airways resulting in permanent airflow obstruction.

The diagnosis of occupational asthma is based on a history of work related reversible airflow obstruction, bronchial hyper responsiveness, and airway inflammation. Symptoms of asthma usually include recurrent episodes of a non-productive cough, chest tightness, wheezing, and shortness of breath. Asthmatic responses to specific occupational agents and symptoms that worsen during work and lessen away from work are indicative of occupational causes of this disease (Chan-Yeung and Malo: 1995; Schenker *et al*: 1998).

An increased prevalence of asthma has not been commonly reported in grain workers (see Tables 5a-g in the Annex), although some have documented an increased prevalence of allergic rhinitis. Allergic rhinitis may occur before the development of allergic asthma and therefore may be a factor in some workers leaving the industry earlier than others. Allergic rhinitis and asthma can develop after exposure to relatively low concentrations of high molecular weight protein allergens. This is in contrast to other types of respiratory conditions such as COPD where exposures in excess of several mg/m$^3$ are required to cause disease.

It has been reported that co-exposure to high concentrations of endotoxin may modify susceptibility to allergic responses to grain dust (Basinas *et al*, 2011). Clapp *et al*: (1993) reported on the effects of challenges with different grain dusts extracts and endotoxin and found evidence that in the first 30 minutes there was a comparable and rapid airway reaction to the grain extracts and to endotoxin resulting in airflow obstruction. This was independent of atopic status or sensitisation to the specific antigens, and occurred mostly in workers with pre-existing severe airway obstruction or non-specific bronchial reactivity. Studies in volunteers who inhaled grain dust provoked mostly non-allergic inflammation in the airways involving accumulation of mucus (Balmes *et al*: 2005) and cytotoxic immune cells (Schwartz *et al*: 1994; Jagielo *et al*: 1996a and 1996b).

Specific inhalation challenge studies have been carried out with grain dust on exposed workers and controls to assess immediate airway responses. These studies recorded both immediate, delayed and biphasic asthmatic airways responses to crude grain or grain dust extract (Chan-Yeung *et al*: 2006). It has been suggested by Anees *et al* (2011) based on serial peak flow analysis that it is possible to differentiate workers with occupational asthma from those with non-occupational asthma as well as those with irritant airway reaction to inhaled grain dust. For the irritant exposed group they took 98 grain-exposed workers (farmers and dock side workers) of whom 40 had no previous asthmatic symptoms. They also included two other groups one diagnosed with occupational asthma and the other a group of non-occupational asthma cases. The criteria for diagnosis of occupational asthma (OA) included a good history suggestive of OA and one of the following: a positive specific inhalation challenge test to an agent to which the worker was occupationally exposed; a greater than 3.2 fold change in non-specific bronchial hyper responsiveness in relation to exposure at work; or the presence of specific immunoglobulin E to an occupational agent with known high specificity. They concluded that work related declines in mean peak expiratory flow (PEF) of 3–4% of the predicted value were unlikely to occur in non-occupational asthmatics or as a consequence of irritant grain dust exposure. However, these acute lung function responses in 'irritant exposed' grain workers were not as severe as those caused by other work related causes of asthma.

Other evidence supporting the occurrence of grain dusts allergy has come from studies of sensitisation in exposed workers. The prevalence of specific IgE to grain dust constituents increases in those exposed to grain dust compared to those not exposed according to Park *et al* (1999a). They investigated grain dust specific IgE and skin prick reactions and bronchial provocation in 43 employees working in the animal feed industry exposed to grain. About 35% of the subjects had work-related skin reactions and ~30% had high specific IgE antibody to grain dust extract. This IgE antibody was detected more frequently in symptomatic workers (40%) compared to asymptomatic workers (11 %) and was significantly associated with atopic status and or smoking. The IgE did not react with house dust mite, storage mite, or corn dust but did react with two proteins from the grain dusts extract. However, this result did not explain why only 40% of the symptomatic patients had raised specific IgE to grain dust extract.

Whilst some have reported evidence of asthma and sensitisation amongst grain workers (Park *et al*, 1998) a paradoxical finding in most studies has been the apparent low prevalence of respiratory allergy (and atopy) amongst the exposed compared to the 'non-exposed' and despite grain dust containing high molecular weight protein allergens.

Studies of apprentice workers in the grain industry showed that those with pre-existing allergy or atopy were likely to develop symptoms (James *et al*: 1990) but left the industry soon after starting their employment (Dosman, JA *et al:* 1991). This may well explain the 'apparent' low prevalence of asthma amongst grain workers (Chan-Yeung: 1990) and has been referred to as a "healthy worker effect". The grain workers who left their jobs at an early stage of employment typically suffered greater annual losses of lung function compared to workers who stayed longer in the industry (Zejda *et al*: 1992). This supported the view that those most at risk were under represented amongst grain workers. A similar observation was made in a study of allergic and atopic farm workers in Sweden who were found to change their jobs more frequently. In contrast, farm owners who developed allergy tended to carry on working because they work in family businesses (Thelin and Hoglund: 1994). Furthermore over long term (13 years) exposure to grain dust Senthilselvan *et al* (2010) noted a longitudinal decline in the prevalence of respiratory allergy but only in grain exposed workers, which supports a healthy worker effect, or acclimatisation.

Other studies have suggested that for some grain exposed workers the risk for atopy and allergy is reduced because of early life exposure to high concentrations of endotoxin. The SUS study in Denmark (Elholm *et al*: 2010) was designed to investigate risk factors for respiratory disorders and changes in lung function among young farming students. A cohort of young Danish farmers (1734 male farming students, 230 female farming students, and 407 army recruits as controls) was established in 1992/1994 and followed up in 2007/2008 (with a participation rate of 51.7%). The study included a cross sectional element at baseline and a case controlled follow up after 5 and 10 years. Even after 5 years of follow up the study showed a lower prevalence of allergy, bronchial hyper reactivity, and immunological sensitisation (measured by skin prick tests and circulating specific and total IgE) in those subjects raised on a farm, compared to those brought up elsewhere. Exposure to endotoxin in adulthood may also reduce the prevalence of atopy and allergy amongst agricultural workers and those working with grain. Basinas *et al* (2011) has shown a protective effect on the development of atopy and asthma in adults in those occupations in which endotoxin levels were persistently raised above 100 EU/m$^3$.

The apparent protective effect of endotoxin exposure on asthma prevalence is not always borne out by studies of farmers (including grain farmers) which have provided evidence of excess numbers of asthma cases. In Sweden a standardized mortality ratio [SMR] of 137 (95% confidence interval of 115–156) was reported for farmers and an SMR of 170 (95% confidence interval of 107– 235) for farm workers (Toren *et al*: 1991). These estimates were adjusted for smoking and compared to a self-reported prevalence of occupational asthma amongst the general population of ~80 cases per million. Amongst female poultry workers and dairy farm workers rates of asthma as high as 602 cases per million have been reported (Toren K: 1996). In Denmark, the prevalence of asthma has been reported as 5.5% in dairy farmers and 10.9% in pig farmers (Iversen *et al*: 1988) and whilst they handle grain feed the observed outcome could be due to other exposures (e.g., animal dander). In France, cumulatively 9.3% of elderly farmers have asthma and 5.9% have current asthma with odds ratios of 2.3 (95% CI 1.0–5.47) for cumulative asthma and 5.35 (95% CI 1.33–21.5) for current asthma in comparison with controls after adjustment for smoking, age, and gender (Neijari *et al*: 1996). It is possible that the 'healthy worker' effect is more likely to influence work preference amongst grain workers (Davies *et al*: 1976) compared to farm workers who typically remain within their communities irrespective of health problems.

*3.2 Chronic Effects of Grain Dust on the Respiratory Tract*

Seasonal grain workers (e.g., in farming) experience a reduction in lung capacity during harvesting work, but this decline typically recovers when harvesting work is completed (Warren CPW *et al*, 1989). The development of chronic phlegm and symptoms of breathlessness during exertion directly relate to the accumulative effects of exposure to grain dust exposures for more than a decade (Huy et al: 1991).

Long term exposure to grain dust (at levels >10mg/m$^3$) has also been shown to cause a progressive decline in capacity of the lung (as measured in terms of FEV1 and FVC changes), although the rate of decline slowed when improved control procedures were introduced reducing the level of exposure to grain dust. Chronic bronchitis is commonly reported in workers employed for many years in the grain industry (see summary table 5a-h). After long periods of exposure cases of interstitial lung disease and obstructive airways disease have been reported. These conditions involve thickening of the connective tissue surrounding the small conducting airways. Inflammatory responses to grain dust may cause tissue remodelling and persistent exposure is also likely to overwhelm the protective mechanisms that clear particulate matter from the airways. Other conditions can develop that include delayed allergic hypersensitivity responses that impair airway gas exchange (Schenker *et al*: 1998; Cosio *et al*: 1978). Exposure to dusts from mouldy grain may cause extrinsic allergic alveolitis (also called hyper sensitivity pneumonitis) and commonly recognised as 'farmers lung disease' in agricultural workers.

3.2.1 Long term decline in lung capacity

Longitudinal studies of workers chronically exposed to grain dust have shown an increased prevalence of cough and phlegm (see summary table 5h) and an accelerated annual decline in lung capacity (Tabona *et al*: 1984; Chan-Yeung *et al*: 1990; Chan-Yeung *et al*: 1992a; Schwartz *et al:* 1995). Bacterial endotoxin in grain dust may be one critical factor causing these symptoms (Schwartz *et al:* 1995, Schwartz DA: 1996), and experimental studies in humans and animals have demonstrated that endotoxin provokes inflammation and airflow obstruction (Gordon *et al*: 1991). In considering the reported declines in lung capacity it is important to recognise that apparently small changes to average FEV1 values can mask larger changes amongst sub-population more affected by the exposure. From this perspective the distribution of changes in lung function is more meaningful along with data on the number showing the greatest functional decline. Tables 5a-h in the annex summarise the available data from different studies as 'group' average changes in lung function where only large shifts in lung function may be highlighted and changes in   more vulnerable groups  missed.

Senthilselvan *et al* (2010) undertook a 13 year longitudinal cohort study of male farm workers (n=263) exposed to grain dust compared to a non-exposed non-farming control group (n=261). They examined changes in FEV1 and FVC over this period and categorised workers exposure to dust based on self-reported job description. They reported significant progressive declines in FVC of ~9.2ml / year amongst those exposed to grain dust compared to non-exposed controls.

Smoking status has also been considered as an important cofactor in declining lung capacity (see table 5e). The prevalence of smoking amongst swine and grain farmers in Canada was shown to be lower (18.3% current smokers) compared to other working groups (30.4% current smokers) (Zejda *et al*: 1993). In contrast more than 30% of grain elevator workers were current smokers, compared to other employee groups (Chan-Yeung *et al:* 1980; Pahwa *et al*: 1994). Whilst there are not comparable recent data on incidence of smoking amongst the GB workforce in this industry, it needs to be recognised that smoking causes a steeper decline in lung function in some individuals exposed to grain dust.

Whilst the inhalation of grain dust over long periods causes a decline in ventilatory capacity both in non-smokers and ex-smokers these declines are greater amongst smokers (Cotton *et al*: 1982; Cotton *et al*: 1983). For those working in the grain industry longer than 20 years, their mean annual loss of FEV1 and FVC was greatest amongst current smokers, followed by ex-smokers and then non-smokers respectively (Pahwa *et al*: 2008). In this twelve-year study, the annual rate of decline in lung capacity increased more during the first few years of employment and then slowed in later years (Pahwa *et al*: 1994). However, this decline was seen in smoking, ex-smoking and non-smoking grain elevator workers and only after the introduction of control measures to reduce dust did the rate of decline in FEV1 and FVC slow down (Pahwa *et al*: 2003).

In a three-year longitudinal study of Canadian grain elevator workers, FEV1 declined more in exposed compared to non-exposed controls (Broder *et al*: 1985; Chan-Yeung *et al*: 1992b; Kennedy *et al*:

1994) but this difference was not observed after twelve years (Chan-Yeung *et al*: 1992b) probably due to a selective loss of symptomatic workers over this period. Studies in Yugoslavia showed increased chronic respiratory symptoms and reduced FEV1 / FVC values amongst smoking and non-smoking grain workers compared to controls (Zuskin *et al*: 1989; Zuskin *et al*: 1992). A significant relationship between ventilatory capacity and dust exposure in grain elevator workers has been reported (Corey *et al*: 1982; Enarson *et al*: 1985), with large declines in FEV1 over a 6-yr period in jobs with high exposures to dust. Long term declines in FEV1 amongst 36% of retired grain workers have also been reported compared to 19% of civic workers (Kennedy *et al*; 1994).

In a six year study of grain workers in Canada (based on a 'nested' case-control study) ~10% of the worst affected workers suffered a decline in their FEV1 (>100 ml/yr) and were exposed to levels of dust >5 mg/m$^3$. Atopy, asthma, bronchitis, or the other respiratory symptoms, were not risk factors for this decline (Enarson *et al*: 1985a). In another study of 454 grain elevator workers their lifetime average exposure to grain dust was determined by collecting air samples over twelve-years and significant dose dependent declines in FEV1 and FVC occurred in those workers with an estimated average exposure between 4 and 9 mg/m$^3$ compared to workers exposed on average to <4 mg/m$^3$ and to non-exposed civic workers. This effect was not related to differences in duration of employment (Huy *et al*: 1991).

There may be distinct mechanisms underlying the long-term responses to inhaled grain dust. In a study in the Netherlands of 390 male workers in the animal feed industry, FEV1 and FVC were analysed over a number of years and related to dust exposure. Workers with prolonged exposure showed reduced values for all flow volume variables except for FVC but those with only a few years of exposure showed a decrease in FVC and peak expiratory flow. In this study steep declines were reported for non-smokers compared to ex-smokers and current smokers (Tielemans *et al*: 1994).

3.2.2 Chronic obstructive pulmonary disease (including chronic bronchitis and emphysema)

Obstructive pulmonary disease is usually progressive and related to abnormal inflammatory response of the lungs to noxious substances such as particles or gases. Conditions such as chronic bronchitis and emphysema are associated with persistent hyper secretion of mucus and loss of efficient gas exchange properties (Balmes *et al*: 2005). This progression of COPD is associated with the accumulation of inflammatory mucous in the lumen of the airways and an infiltration of the lining of the airways by immune cells. These changes are coupled to a repair / remodeling process in response to the effects of hazardous fumes and dusts which can lead to a thickening of the walls of the airways (Hogg *et al*: 2004). The American Thoracic Society in 2002 issued an official statement about the occupational contribution to the burden of airway disease in which it concluded that about 15% of asthma and COPD is likely to be related to hazardous exposures in the workplace (Balmes *et al* 2003).

Longitudinal studies of workers chronically exposed to organic dusts like grain and cotton have shown an increased prevalence of cough and phlegm and an accelerated annual decline in lung function. This response is primarily mediated by non-allergic inflammatory mechanisms and bacterial endotoxin although other cofactors cannot be excluded. Grain dust can activate these inflammatory responses and promote an influx of phagocytic cells into the upper and lower airways (American Thoracic Society Statement: 2003).

In a large cross national study of the risk factors for COPD, Lamprecht *et al* (2011) analysed data from studies in 14 countries in which participants aged ≥40 years were recruited and completed spirometry tests and a questionnaires about their respiratory symptoms, health status, and exposure to risk factors for COPD. Diagnosis of COPD was based on the Global Initiative for Obstructive Lung Disease (GOLD) guidelines. The study found a significant proportion of COPD amongst never smokers with 6.6% meeting the criteria for mild COPD, and 5.6% meeting the criteria for moderate to very severe COPD. The predictors for COPD in never smokers were age, education, occupational exposure, childhood respiratory diseases, and body mass index alterations. Exposure to organic dusts was identified as a risk factor with 22.0% of non-smokers reporting at least 10 years of exposure. The odd ratio (OR) estimates (OR =1.96, p<0.007) for women exposed to organic dust were statistically significant.

Chronic bronchitis has been defined as the daily production of phlegm for at least three months in a year and for at least two consecutive years. It is a common symptom amongst grain workers and is caused by inflammation and excess production of mucous (sputum) in the airways. Chronic bronchitis and chronic airflow limitation have been reported amongst those persistently inhaling high levels of grain dust (see summary table 5a-g) or mouldy farm dust (Terho *et al*, 1987; Terho E 1990; Dalphin *et al*: 1993) and is a cause of significant respiratory morbidity. In an analysis of four large European epidemiological studies of endotoxin exposed workers, the risk of chronic bronchitis was found to be dose related above concentrations of 100 endotoxin units (EU) / $m^3$ (Basinas *et al:* 2011). Cigarette smoking is a major risk factor for the development of obstructive airway disease and many of the symptoms associated with smoking overlap with those caused by inhalation of grain dust (e.g., chronic bronchitis).

In a study of 90 grain workers compared to 90 'non-exposed' subjects from the local community (both groups were lifetime non-smokers), the prevalence of chronic bronchitis was significantly higher (23.1%) amongst the grain workers compared to the controls (3.3%); and grain workers had reduced expiratory flow rates suggestive of airflow obstruction. Smoking in isolation was seen as a major risk factor for the development of chronic bronchitis, having an additive effect with agricultural dust exposures (Melbostad *et al*: 1997; Dalphin *et al*: 1998). However, it has been concluded that inhalation of grain dust by non-smokers is sufficient to increase their risk for bronchitis in a time and exposure dependent way (Dosman *et al:* 1980; Kirkhorn and Garry: 2000).

In the twelve-year study in the Canadian grain industry, groups of several thousand workers at large grain facilities were investigated to determine the prevalence of sputum production, wheeze, cough, and shortness of breath. Shortness of breath and excess sputum production was reported by approximately 30% of the workers during the first nine years of this study. During this period it was found that approximately 80% of all of the dust exposure measurements were less than 10mg/$m^3$ and 60% of all of these measurements were below 5mg/$m^3$. Following the improvement of controls to reduce dust exposures the proportion of staff reporting shortness of breath and excess sputum reduced to ~11% (Pahwa *et al*: 2006) (see table 5h).

Many other studies have reported a high prevalence of chronic bronchitis in grain workers. In one study 37% of grain workers had bronchitis and in those who were smokers the prevalence was 42% significantly higher (p<0.01) compared to 30% prevalence for non-smokers. These symptoms were consistent with acute and chronic inflammation of the airways. A clear association with atopic status and allergic disease was not established but the authors considered that a healthy worker effect (i.e. loss of workers with allergy at an early stage of their career in grain handling) might have accounted for this (doPico *et al*: 1977). As a whole these studies of grain handlers reported a variation in the prevalence of chronic bronchitis between 23 and 37% (doPico *et al*: 1977; Dosman *et al*: 1980; McDuffie *et al*: 1991; Huy *et al*: 1991) with cigarette smoking having a significant additive effect (doPico *et al*: 1977; Chan-Yeung *et al*: 1981).

3.2.3 Extrinsic allergic alveolitis

Microbial constituents (particularly fungal spores) in damp grain can also cause a delayed hypersensitivity reaction called extrinsic allergic alveolitis (commonly referred to as 'farmer's lung' amongst agricultural workers). However, with the implementation of better systems to harvest, transport and store grains, conditions that give rise to the growth of thermophilic microorganisms (warmth and high humidity) occur less commonly and so cases of EAA amongst grain workers are not common.

A variety of antigenic agents found in mouldy hay, grain or straw are thought to cause extrinsic allergic alveolitis including thermophilic *Actinomyces spp.* and certain *Aspergillus* fungi (Schenker *et al*: 1998; Linaker and Smedley: 2002). Farmers' lung has been most associated with exposure to *Saccharopolyspora rectivirgula*. Acute episodes of Farmers lung are associated with symptoms of breathlessness, cough, fever and chills that occur several hours after exposure and subside within a

few days. A sub-acute form exists in which there is a gradual development of breathlessness over weeks and months with recurrent acute attacks and chronic and productive cough. This is caused by a delayed allergic reaction involving cell mediated toxicity and in some individuals raised concentrations of precipitating antibodies and immune complexes in the circulation. These immune complexes can also lead to the formation of tissue granulomas. In the acute phase a heavy influx of the gas exchange surfaces (i.e. the alveoli) by large numbers of lymphocytes is common. If this persists progressive fibrotic changes can occur in the lung leading to irreversible damage (Linaker and Smedley: 2002).

In those already sensitised symptoms may appear within hours of inhaling mouldy grain or straw, and may persist at least a day after exposure at which point the fever subsides but shortness of breath persists. These symptoms are similar to ODTS, but individuals with EAA are often characterised by progressive weight loss and shortness of breath and their symptoms are provoked by exposure to low levels of mouldy dust. The progression of EAA symptoms also vary between individuals and may be acute, sub-acute, or chronic (Boyd *et al*: 1982). As a consequence the diagnosis of EAA is challenging because many of the symptoms and tests are sensitive but not of specific diagnostic value.

There are fewer reports of grain related EAA cases but studies of Farmers lung have shown that a third of them report persistent symptoms and even amongst asymptomatic individuals there is evidence of physiological impairment of airway function due to fibrosis or emphysema (Linaker and Smedley: 2002). In a study of farmers, of 86 suspected cases of EAA, 65% had a history of symptoms after 5yrs and 40% sustained residual respiratory dysfunction (Mönkäre and Haahtela *et al*: 1987). In a six-year study of 33 farmers with suspected EAA, 16 retained lung function within normal ranges, and 13 suffered shortness of breath with the remainder showing a variety of other symptoms (Lalancette *et al*: 1993).

In contrast to ODTS for which a single high dose exposure to mouldy grain may be sufficient to provoke symptoms, in EAA symptoms occur after prolonged periods of exposure to high concentrations of mould.

A more complex relationship exists with smoking as a risk factor for EAA. For conditions like chronic bronchitis, exposure to grain dust and smoking status increase the prevalence of symptoms. Whereas in EAA fewer cases are found amongst smokers than non-smokers, and non-smokers are over represented amongst cases of EAA (Hapke *et al*: 1968, Roberts *et al*: 1976; Warren: 1977). Non-smokers also appear more at risk of sensitisation (i.e., developing allergen specific IgG) (Morgan *et al*: 1973; Morgan *et al*: 1975). This apparent protective effect may be due to cigarette smoke enhancing innate cytotoxic responses leading to an inactivation of microbial spores (Barbers *et al*: 1991).

*3.3 Susceptibility and gender differences in response to grain dust*

Recent studies provide evidence that the impact of exposure to organic dusts differs between men and women. Some of these studies have addressed exposure to organic dusts in general of which grain is only one contributory factor and therefore these studies do not provide definitive evidence of gender differences amongst grain exposed workers.

In an analysis of data from 12 previously published studies, Schachter *et al* (2009) examined results from 3011 workers exposed to organic dusts (1379 female and 1632 male) with a control group of 806 workers not exposed to organic dust (male = 419, female = 387). A high prevalence of acute and chronic respiratory symptoms were found in the groups exposed to organic dusts compared to the controls but there was significantly less chronic cough, chronic phlegm and chronic bronchitis in women compared to men (after adjusting for smoking, age and duration of employment). Upper respiratory tract symptoms were in contrast more frequent in women than in men as was the prevalence of occupational asthma which varied from 1.1% to 10.5% in female workers and from 1.2% to 7.4% in male workers. This observation was reported to be consistent with the findings from other published studies suggesting elevated prevalence of asthma in females exposed to organics dusts compared to male workers similarly exposed. Significant reductions in acute lung function (FEV1, FVC and FEF) were found in males exposed to textile dusts and smaller reductions in female workers.

Amongst male and female agricultural workers significant changes in lung function were not observed.

A more relevant example is the study by Dimich-Ward *et al* (2012) who examined gender differences in respiratory health amongst workers exposed to organic and inorganic dusts based on meta-analysis of 12 occupational health studies involving 1,367 women and 4,240 men. The majority of those considered under the organic dust category were farm residents exposed to grain dust, grain terminal workers but it also included sawmill workers (i.e., wood dust). With organic dust exposure, men had elevated odds for occasional wheeze and worse lung function compared to women. However, for women they had higher odds ratios for shortness of breath whether they were exposed to inorganic dusts (i.e., not organic dusts) or had no occupational exposure. The highest adjusted odds ratios for women were for asthma (OR = 8.38, 95%CI = 1.72-40.89) but only amongst the exposed group.

Whilst these studies have examined in general terms the impact of gender and exposure to organic dusts none of them examined groups only exposed to grain dust. Therefore, for the studies already undertaken it is not clear whether the differences in gender reported are due to physiological mechanisms or the nature of the specific workplace exposures (i.e, tasks undertaken and exposure history).

*3.4 Relationship between exposure and risks for respiratory disease*

There are a large number of published studies on exposure to grain dust and the risk for respiratory disease. The majority of these studies were carried out in Canada and the United States where this part of their agricultural industry is very large and employs many people. Comparable studies in the UK are smaller and often lack age and sized matched control 'non-exposed' populations; although a number of larger systematic studies have been conducted in Holland. It is possible that the results of the Canadian and US studies are not comparable to the UK industry (e.g., volumes of grain handled, scale of operations in grain stores etc.), however, many of these overseas studies are robust in their design (i.e. large size of the study population, control groups, measurement of exposure to grain dust, consideration of smoking status and other contributory factors). These studies have been discussed in the body of this report and the overall results are summarised in Tables 5a-h in the annex.

The schematic in Figure 2 generalises these various findings to provide a framework for thinking about the role of the different hazards in grain dust, the importance of exposure dose and duration of exposure and the development of symptoms and disease. It also takes into account what has been found about the effects of predisposing factors such as history of atopy, pre-existing allergy, smoking, and the nature of the work exposure. The remainder of this section explains possible relationships between exposure to grain dust and the risk for development of respiratory disease.

It is very likely that most of the acute responses are due to the irritant effects, or an innate immune response to e.g., bacterial toxins. The responses can be triggered within minutes but may persist. In the case of ODTS this response is specifically caused by very high concentrations of bacterial endotoxin and with the implementation of better grain storage facilities is less likely to occur. Other acute responses may be based upon physiological reactions to grain dust resulting in a work 'shift' related decline in lung capacity. It has been suggested that these effects may be mediated by inflammatory molecules released within the airways in response to grain dust.

It is likely that irritant and inflammatory reactions to grain dust stimulate mucous secretion and an increased prevalence of bronchitis. However, it should be noted that a progressive improvement in symptoms of bronchitis were found in retired workers no longer exposed to grain dust (Kennedy *et al*: 1994).

Evidence for acute dose related effects of grain dust in reducing lung function have been presented by doPico and associates (doPico *et al*: 1983) who conducted a study of exposure to grain dust during an 8-hour work shift for 248 workers. The total dust concentration for the 8-hour shift was measured by personal air sampling. This dose-related decline in lung function was observed irrespective of smoking habit, atopic status or age. The mean total dust level was relatively low ~3.0 mg/m$^3$ suggesting that acute and chronic respiratory effects occurred at concentrations below 10 mg/m$^3$.

Whilst there is less evidence specifically demonstrating that work in the grain industry is a specific risk factor for development of COPD (or asthma), there is sufficient evidence that prolonged exposure to grain dust reduces lung capacity at a rate faster than age related declines. Many of the studies have reported on the acute effects of inhaled grain dust demonstrating shift related (see Table 5g) increases in the prevalence of symptoms such as cough, phlegm, and nasal congestion. Other cross sectional (see Table 5f) and longitudinal studies (see Table 5h) have demonstrated exposure dose relationships with declines in lung function comparable to the effects of regular smoking (see Table 5e, d & f) accompanied by an increased prevalence of upper and lower airway congestion. These studies have demonstrated an additive deficit on lung function for those workers exposed to grain dust and who smoke.

There are a number of studies highlighted in the report because of the size of the study population and the duration they were followed. In particular the Canadian 12 year longitudinal study of large groups of grain elevator workers (see Table 5h) which was part of the Canadian Grain Dust Medical Surveillance Programme. This study included 5 cycles (~every 3 years) for which grain dust levels were monitored and groups of several hundred workers from each of five regions of Canada were monitored for symptoms and lung function. During this period when average exposures reduced for some groups (e.g., smokers) there were corresponding improvements with fewer respiratory symptoms reported as well as slowing down in the rate of decline of lung function. This study provided key information about the long-term changes to airway function and how these related to dose and duration of exposure and smoking status.

Dimich-Ward *et al* (2011) evaluated respiratory health in two cohorts of grain terminal elevator workers who participated in respiratory health surveys in 1978 and 2008. Symptoms were reported using questionnaire and spirometry tests undertaken on 584 workers from the baseline (1978) survey and 215 workers from the 2008 survey. Using logistic regression and general linear modelling they demonstrated that between these two times (30 years) static area samples of grain dust averaged 8.28 mg/m$^3$ in 1978, reducing to 2.06 mg/m$^3$ by 2008. Workers in 1978 survey had a significantly higher prevalence of respiratory symptoms (an OR of 3.78 [95%CI = 2.07–7.25] for shortness of breath), and a lower prevalence of atopy and mean lung function capacity. They concluded that the overall health of these workers improved with progressive reductions in grain dust exposure.

The long term risks for respiratory disease that occur with exposure to grain dust have been examined by Karunanayake *et al* (2011) who studied a population of 871 adults living in rural Saskatchewan. This cohort participated in two cross-sectional respiratory studies conducted ten years apart (in 1993 and 2003). The study was based on the use of symptom questionnaires (respiratory symptoms of cough, phlegm and wheeze), history of allergy, smoking, and information about the home and farm environments. Modelling was used to assess the longitudinal outcomes such as cough, phlegm and wheeze arising from the previously reported symptoms. Individuals who were asymptomatic at the start of the study were assessed as to which factors were associated with the development of symptoms by 2003. During this period in those exposed to grain dust there were significant increases in the prevalence of cough (0.35% increase per year; p=0.02), wheeze (0.46% increase per year; p=0.007) and phlegm (0.33% increase per year; p=0.026). Not surprisingly, smoking status in 1993 was associated with cough and phlegm in 2003. Amongst the subjects that were asymptomatic in 1993, 13.4% developed cough, 12.3% phlegm and 19.1% wheeze by 2003. In terms of factors that contributed to risk of symptoms 10 years later, older subjects experienced more symptoms, as did ex-smokers and current smokers, and those who at baseline reported living in damp homes and having allergic reactions to inhaled allergens.

Longitudinal studies that followed grain workers demonstrated that large declines in respiratory capacity occurred only amongst those exposed for many years to concentrations of dust greater than 10mg/m$^3$. Huy *et al* (1991) examined grain-dust exposure and changes to lung function in the 12-year longitudinal study amongst a group of 454 grain workers at a facility in Vancouver. They divided the workers into three groups according to their mean exposure level: high exposures being more than 9 mg/m3; intermediate being 4 to 9 mg/ m3 and low less than 4 mg/m3. The workers in the high-exposure group had the greatest decrease in FEV1 (34.1 ml-1 per year).

Respiratory conditions such as bronchiolitis obliterans and EAA are also a result of chronic exposure to grain dust but are dependent upon specific circumstances in which damp and warm environmental conditions promote high concentrations of micro-organisms (such as fungal spores) which trigger delayed immune hypersensitivity reactions when inhaled. These outcomes are less likely to occur today because of the economic imperative on farmers to maximise the yield of grain that is safe for food production.

**Figure 2:** Schematic showing relationship between exposure to grain dust and duration of exposure in relation to the types of symptoms reported amongst grain workers.
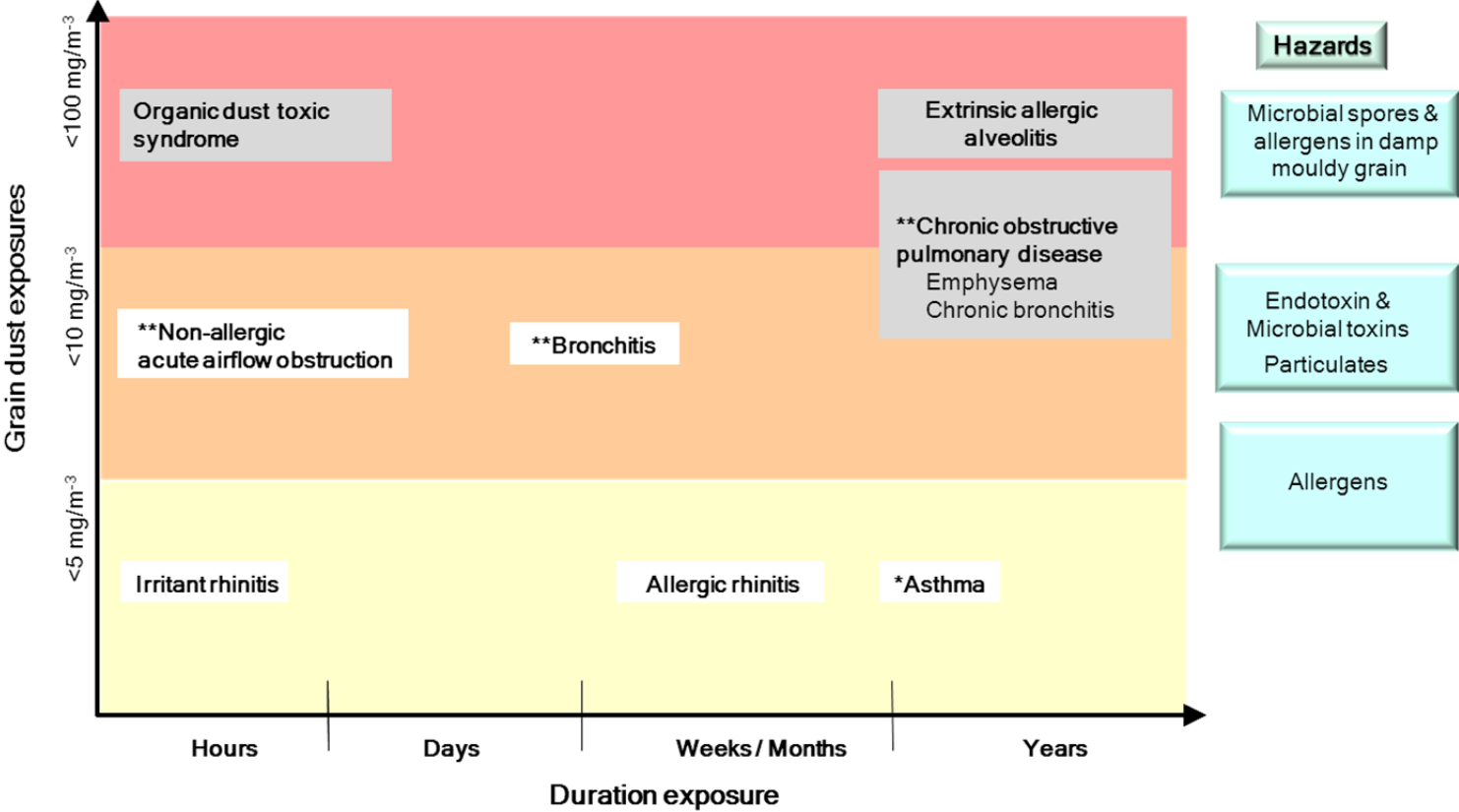
# 4.0 APPENDICES

## 4.1 Appendix 1: Summary of hazardous constituents in grain dust

Grain dust has been referred to as a 'nuisance dust' a term that does not take into account the complex mixture of inorganic and organic constituents and their distinct toxicological irritant, inflammatory and allergic effects. Of the different types of grain, in worker surveys, most considered barley dust (70-90%) and oat dust (35-53%) especially irritating to the airways; this is probably related to the finer particle size in the dust derived from these two crops. Most symptoms caused by grain dust appear to be attributable to irritant and cytotoxic responses coordinated by the innate immunity and paradoxically the prevalence of allergic disease is low amongst grain workers despite grain dust containing many allergens (Farant and Moore: 1978, Manfreda *et al:* 1986).

The main constituents of grain dust are proteins derived from the host plant, from other plants, and from insects, arthropods, animal detritus, and a host of microorganisms. The dust also contains a complex soup of natural and 'man made' chemicals (e.g., pesticides and fertilisers). A proportion of the dust is inorganic fine silica and quartz particles. Wijnand *et al* (2012) has recently summarised the evidence about the setting of occupational exposure limits for organic dusts as well as the methodology required to undertake such assessments. This review emphasises that these dusts are complex mixtures of biohazards from bacteria, fungi, microbial toxins (such as endotoxin), allergens and inorganic constituents. The following section summarises the toxic effects of these constituents.

### 4.1.1 Bacteria and fungi

The microbial content of grain dust consists of a wide variety of fungi and bacteria but the variety of organisms depend on the crop, the growing season, the water content and the storage temperature of grain. These organisms contaminate grain when it is growing in the field and when it is stored (Lacey: 1994a and 1994c Lacey and Dutkiewicz: 1994b; NIOSH 1986). Common fungi on growing crops include *Cladosporium sps, Alternaria sps, Fusarium sps, Rhizopus sps* with prominent bacteria such as *Pseudomonas sps, Streptomyces sps*, and *Erwinia herbicola* (NIOSH 1986). In stored grain the number of field organisms declines and other types of fungi and bacteria (Lacey: 1980) like *Aspergillus sps* and *Penicillium sps* predominate under dry conditions whereas organisms like *Micropolyspora, Thermoactinomyces vulgaris* (NIOSH 1986) predominate in damp conditions.

A comprehensive assessment of the microorganism content of grain and agricultural dust was recently reported (Swan *et al*: 1998; Swan *et al:* 2007). The microbial content varied from a few million viable bacteria to excess of $10^7/m^3$. Numbers of fungi in excess of $8 \times 10^6$ were also recorded. In another study, the total number of organisms including spores was found to be as high as $10^9/m^3$ with peak exposures of $10^{10}/m^3$ organisms (Schenker *et al*: 1998). Assaying viable microorganisms also underestimates the total exposure (i.e., live and dead) such that counts in excess of $10^8/m^3$ viable and dead bacteria can be found in heavily contaminated dust. Viability is not the key aspect driving inflammatory reactions; dead microorganisms release toxins that stimulate immune reactions.

More recently a large study has been conducted in Poland by Gora *et al* (2009) of 10 facilities engaged in herb and grain processing, flax threshing, grain storing, baking, and cereals production. They reported dust concentration ranging from 0.18 mg/m$^3$ to very high levels of ~87mg/m$^3$ and the total concentrations of viable airborne microorganisms ranged from 0.2–861×10$^3$ cfu/m$^3$. The highest concentrations of levels of airborne micro-organisms were recorded at flax farms, in grain elevators and in herb processing plants.

The concentration of Gram negative bacteria ranged from 0.0–168×10$^3$ cfu/m$^3$ and they formed between 0 – 48% of the total count. The concentration of endotoxin was large and ranged from 0.004–1563µg/m$^3$ and this correlated with the concentrations of Gram-negative bacteria, total microorganisms, and peptidoglycan. Muramic acid, the chemical marker of peptidoglycan, was detected in 9 out of 13 (69.2%) samples and the concentration ranged from 1.93–416 ng/m$^3$.

Gram-positive bacteria and fungi were detected at all sampling sites and their median concentrations were respectively 18×10$^3$ cfu/m$^3$ and 0.66×10$^3$ cfu/m$^3$ respectively. Of these Gram-positive bacteria

constituted between 23–93% of the total microbial count with the common species being *Pantoea agglomerans* which was found in most samples along with *Staphylococcus spp., Curtobacterium pusillum, Rhodococcus fascians, Aureobacterium testaceum, Sanguibacter keddieii, Microbacterium spp.,* and *Bacillus spp*. The concentration of peptidoglycan was correlated with the concentration of Gram-positive bacteria. The concentration of thermophilic actinomycetes ranged from $0.0–1.45\times10^3$ cfu/$m^3$ and fungi constituted 2.5–76.9% of the total microbial count and included common species such as *Penicillium spp., Mucor spp., Alternaria spp., Aspergillus niger,* and *Aspergillus spp*.

The dust concentrations were high in the grain processing facilities which involved handling sacks (median = 20.57 mg/$m^3$) and lower in grain elevator activities (median = 6.27mg/$m^3$) and endotoxin concentration were amongst the highest (median = 156μg/$m^3$) for some activities such as handling unwashed grain. The authors noted that high the dust concentration in the current study were still 1-2 orders of magnitude lower than those recorded 30-35 years ago in Poland. Whilst the results of this study may not be representative of farms in the UK (for reasons of climate and farming practice) the study provides an up to date assessment of different micro-organisms in relation to concentrations of different microbial toxins. The samples for this study were collected by area high volume sampling (50 litres /min) and therefore do not represent a measure of personal exposure.

The type and number of microorganisms varies depending on the crop, the climate, and the season, however, for many crops the dominant microorganisms are stable. Damp conditions are necessary for the growth of thermophilic moulds and bacteria some of which cause respiratory allergy. Large differences between species have been found reported for freshly harvested grain compared to stored grain and comparing grain used human and animal consumption. Microorganisms found in grain at harvest include saprophytic fungi (e.g., *Alternaria* spp., *Cladosporium* spp.) and bacteria such as *Pseudomonas spp* and *Enterobacter agglomerans* (Dutkiewicz, 1978; Lacey, 1980). Aerobic gram-negative microaerophilic rods and cocci as well as gram-negative facultative anaerobic bacteria (*thermoactinomycetes* and *actinomycetes)* are prevalent bacteria in agricultural bioaerosols.

Numbers of *Aspergillus flavus* can be low in fresh grain but in stored grain a different range of microorganisms are typically observed depending on the water and oxygen content, and the storage temperature. Dry storage conditions preserve the quality of grain and at 12-13% water content most microorganisms do not proliferate. When the water content increases above this level the spores of 'storage fungi' (e.g., *Aspergillus spp*., and *Penicillium spp)* germinate (Lacey, 1980). Excessive damp conditions lead to active microbial growth, which raises the temperature of stored grain as high as 65-70°C promoting thermophilic and thermotolerant fungi (e.g., *Actinomycetes* species) and the thermophilic bacteria (e.g., *Penicillium* spp and *Bacillus* spp, *A. flavus*) (Darke *et al*, 1976; Lacey and Dutkiewicz: 1994b). Storage conditions for animal feed grain may be less stringent and high numbers of *A. candidus* and *Penicillia* have been reported including *Saccharopolyspora spp* which has been identified as a causative agent in farmer's lung disease (Schenker *et al,* 1998)

Inhalation of large numbers of microorganisms can cause respiratory symptoms irrespective of whether they are able to grow in the airways. Many microorganisms shed toxins that provoke inflammatory reactions activating cytotoxic cells such as neutrophils and the alveolar macrophage. These macrophages are present in large numbers in the alveoli and act as the first line of defence against pathogens by containing and / or degrading inhaled particulates. Innate immune response to microorganisms are coordinated by specific signalling pathways (e.g., the Toll receptor family) (Medzhitov: 2000) that stimulate cells lining the airways to release crisis signals called cytokines (Johnston *et al*: 1998). These cytokines recruit more macrophages and neutrophils from the peripheral circulation to the sites where bacterial toxins reside within the lung.

Cytotoxic factors released by phagocytic cells are designed to destroy pathogens but also stimulate other defence mechanisms. For example neutrophil derived proteases and free radicals stimulate the fluid and mucin secretion (Steiger *et al:* 1995). This hypersecretion response contributes towards obstruction of the airways and when prolonged can result in increased numbers of Goblet cells that secreting mucin into the airways (Beckmann *et al*: 2002). Microbial toxins also induce changes to the sulphation of mucins (increasing their negative charge) (Shimizu *et al*: 2001). High concentrations of

free radicals produced by neutrophil are reported to compromise mucociliary clearance of particles from the airways (Rogers DF: 2001). The inflammatory reaction to microorganisms and their toxins is therefore a significant component of the response of the airways to inhaled grain dust.

4.1.2 Endotoxin

Airborne and settled grain dust contains endotoxin whose content varies throughout the seasons being lowest in January and highest in November; the respirable and settled dust also contain significantly higher endotoxin content in September and October (Wirtz *et al*: 1984; DeLucca and Palmgren: 1987).

Endotoxins are heat-stable lipopolysaccharide (LPS) protein complexes that are part of the outer membrane of Gram-negative bacteria. LPS is amphipathic (i.e., ability to cross lipid membrane) consisting of lipid-A and polysaccharide with hydrophilic properties (i.e., soluble in water). They are released from the cell by bacteria such as *Enterobacteriaceae, Rhodospirillaceaei* and *Pseudomonadaceae* (Burrell R: 1990; Rietschel *et al*: 1985) and persist in dust for long periods.

Endotoxin is one type of microbial toxin (see later section) but may be a key factor responsible for obstruction and inflammation in the airways caused by grain dust. Concentrations of endotoxin in grain dust up to 190,000 EU $m^3$ have been reported with the highest personal exposure levels for tasks such as loading grain at docksides and harvesting grain (Swan *et al*: 2007). Higher concentrations have been reported in damp and freshly harvested grain compared to dry grain (Halstensen *et al*: 2007).

The concentration of endotoxin in determined using the Limulus amoebocyte lysis method, in which endotoxin causes the lysis of amoebocytes (a blood cell found in *Limulus* the Horseshoe crab) generating a coloured reaction. The detection limit is ~0.05 EU/$m^3$ for kinetic chromogenic endotoxin assays (Schenker *et al:* 1998). As a functional activity assay considerable variation is reported between standard preparations of endotoxin, and results are expressed in units of activity not mass.

Endotoxin has been recognised as an important factor in the aetiology of occupational lung disease (Dutch Expert Committee on Occupational Standards; 1997; Douwes and Heederik: 1997). Studies of occupational exposure to cotton dust suggest that respirable endotoxin is more predictive for respiratory symptoms and airway obstruction than gravimetric measurements of the dust (Castellan *et al*: 1984). Inhalation of endotoxin causes decreased airflow even amongst those not previously exposed (Michel *et al:* 1989; Rylander *et al*: 1989; Schwartz: 1996) and high doses of endotoxin cause acute fever, shivering, dry cough, shortness of breath, and chest tightness (Rylander *et al*: 1989; May *et al*: 1986; Von Essen: 1990). The impact of endotoxin on lung function is dose dependent with reductions to the forced vital capacity (FVC), forced expiratory volume (FEV1), variable airflow, and acute loss of diffusion capacity with bronchial obstruction. Volunteer studies support the conclusion of the epidemiology studies, and inhalation challenges with endotoxin caused dose dependent reduction to FEV1 and FVC, as well as increased congestion (Schenker *et al:* 1998)

Inhalation challenges with endotoxin up to 1,000 to 2,000 ng/$m^3$ provoke systemic fever, chill, breathing difficulties and fatigue. Levels of endotoxin of 100 to 200 ng/$m^{-3}$ cause acute bronchoconstriction, whereas doses of 20 to 50 ng/$m^3$ cause irritation of airways. Some individuals are more sensitive to endotoxin and doses as low as 10ng/$m^3$ were reported to cause inflammation (Rylander and Peterson: 1993).

Inhaled endotoxin causes profound inflammation activating alveolar macrophages and recruiting neutrophils and doses of endotoxin comparable to those found in grain dust causes a rapid recruitment of neutrophils into the airways in murine models (Gordon *et al*: 1991). This also results in the release of pro-inflammatory cytokines like tumour necrosis factor (TNF$\alpha$/$\beta$) that promotes systemic fever and interleukin-8 (IL-8) that recruits neutrophils (Chensue *et al*: 1991; Strieter *et al*: 1993).

Polymyxin B (a chemical that binds tightly to endotoxin) has been used to deplete the endotoxin in grain dust. In mouse inhalation models, dust depleted of endotoxin caused a significantly (but not completely) reduced inflammation compared to non-depleted dust (Jagielo *et al*, 1996a). Mice genetically deficient in the signalling pathway for endotoxin responded less acutely when challenged with grain dust and did not develop chronic remodelling of the airways. In contrast wild type mice

without the defective response to endotoxin developed persistent hyper-reactivity and airway remodelling (Schwartz *et al*, 1994). In mice sub-chronically exposed to endotoxin immune cells accumulated underneath the airway accompanied by changes to the connective tissue that persists once the inflammation had resolved (Jeffrey *et al:* 1989).

Endotoxin has been found to influence the response to allergens. In allergic airway disease concentrations of endotoxin encountered in the domestic setting increased the severity of asthmatic episodes (Michel *et al***:** 1991; Michel *et al* 1996). Asthmatics also develop airflow obstruction at low concentrations of inhaled endotoxin (Michel *et al*, 1989) and bronchial reaction to inhaled allergens occurs more readily in the presence of endotoxin (Dubin *et al,* 1996).

4.1.3 Other microbial toxins

Endotoxin is not the only bacterial toxin in grain dust. The membrane of Gram-positive bacteria contains peptidoglycans that provoke inflammatory responses in experimental models. FMLP (formyl-met-leu-phe peptide) is a potent chemoattractants for neutrophils; bacterial heat shock proteins and superantigens activate cytotoxic T-lymphocytes; (Rylander and Peterson: 1993; Kumar *et al:* 1993; Dannecke *et al*: 1994); *Pseudomonad* species produce exotoxin-A in damp conditions; and some bacteria produce plant phytotoxins that are toxic to humans.

*Penicillium sps, Aspergillus sps, Alternaria sps, Actinomyces sps* and *Mucor sps* are common reported fungi growing in stored grain and their abundance depends on temperature and humidity. High molecular weight glucose polymers like $(1\rightarrow3)\beta$-D-glucans in fungal cell walls provoke inflammation in the respiratory tract (Rylander and Peterson: 1993; Fogelmark *et al*, 1984; Eduard *et al*: 2001). Fungi also produce mycotoxins that have a wide spectrum of toxicity in animals and humans. For example, *Fusarium* infects many grain crops producing fumonisins, fusarins, T2 toxin and other trichothecenes. Moist corn in commercial feed has levels of fumonisins as high $\sim500\mu g/g^{-1}$ (Thiel *et al*: 1991), and mycotoxins like trichothecenes and spores of *Stachybotrys atra* (Croft *et al*:  1986) cause acute illness (Bacon *et al*: 1989; Plattner *et al*: 1989; Ramakrishna *et al*: 1989).

4.1.4 Pesticides

Common pesticide residues in grains include herbicides, insecticides, molluscicides, acaricides, fungicides, rodenticides, and biocides. The majority in use are synthetic organic compounds (e.g., organophosphates, synthetic pyrethroids, and triazine herbicides). The main risks for exposure relate to preparation from concentrated stocks (i.e., for dermal exposure) or close proximity during application by spraying (i.e., inhalation exposure).

In one cross-sectional study conducted in Canada, use of carbamate insecticides was significantly related to the prevalence of asthma in a population of male farmers (Senthilselvan *et al:* 1992); a few case reports have also documented asthma symptoms after exposure to organophosphate insecticides (Bryant: 1985; Deschamps *et al*:, 1994) and fungicides (Honda: 1992; Royce *et al*: 1993; Sprince *et al*: 2000) However, these cases were associated with the application of concentrates and not the residues found in grain. Pesticides may be applied later during grain storage to control growth of microorganisms and pests (Schenker *et al*: 1998; Kirkhorn and Garry: 2000) in which case the risk for exposure by inhalation is increased.

4.1.5 Exposure to Inorganic Content of Grain Dust

The respiratory toxicity of silica dust has been widely studied (American Thoracic Society Committee: 1997) but the silica in soil dust is regarded as less pathogenic than dust from mining and quarrying. There is a significant inorganic component to grain dust (~15-43%) and during processing of grain this content reduces (Donham K: 1986). Silica particles provoke inflammation by generation of free radicals at the surface of the cells lining of the lung, and when inhaled in high concentrations overload the alveolar macrophage clearance mechanism. This leads to the formation of 'giant cells' and expression of cytokines that promote deposition of connective tissue and fibrosis (Schenker *et al*: 1998).

4.1.6 Allergens and immune hypersensitivity

The prevalence of allergic respiratory disease in grain workers is low despite grain dust containing high molecular weight protein allergens and low molecular weight chemical allergens. High molecular weight protein allergens (microbial, plant or animal) typically cause a type I immediate hypersensitivity characterised by increased circulating levels of specific IgE; a process termed sensitisation. The production of IgE is not sufficient to cause allergy and hypersensitivity reactions only occur when basophils and mast cells are triggered to release histamine (and other mediators) by a complex between the IgE and the allergen; binding of this complex to receptors on the surface of mast cells and basophils triggers the release of molecules that initiate the allergic reaction.

Sensitisation is demonstrated by quantifying levels of allergen specific IgE using immunoassays. It can also be demonstrated by skin tests in which the allergen is either injected into the skin (for high molecular weight allergens) or placed on the surface of the skin (for chemical allergens). Skin challenge tests are a functional measure of allergic sensitisation demonstrated by the appearance of wheals at the site of contact; and are used to demonstrate immediate and delayed reactions.

4.1.7 Allergens

**Microbial allergens**: Microorganisms in grain dust cause respiratory allergy (e.g., *Aspergillus spp.*, *Cladosporium spp*, *Alternaria spp* and *Penicillium spp.*) (Darke *et al*: 1976; Dutkiewicz *et al:* 1985; Lacey 1994c) and specific microbial products (e.g., enzymes) are potent allergens (e.g. bacterial amylase, glucosidase, subtilisin-like proteases, fungal amylase and cellulose, etc.) (Baur X: 2005).

**Insects and storage mites**: Careful management of grain stores is required to prevent growth of storage mites, which typically flourish in humid and warm environments (Platts-Mills and de Weck: 1989). Numbers of mites between 1,000–10,000 per gram of grain have been reported (Leskinen and Klein: 1987) levels much higher than encountered for domestic settings (Korsgaard: 1983; Harving *et al*: 1993).. Storage mite such as *Acarus sps*, *Lepidoglyphys sps*, *Gypcyphagus sps* cause type I allergic reactions but are usually more common in warm, humid, and mouldy environments (Terho *et al*: 1985; American Thoracic Society. Respiratory health hazards in agriculture: 1998; May *et al*: 1996). Mite excreta contain many allergens such as proteases and blood proteins, and the excreta are sufficiently small to become airborne when disturbed. However, not many cases of grain workers sensitised to arthropod / insect allergen have been reported; an exception was a case of respiratory allergy attributable to the grain mite *Glycyphagus destructor* (Davies *et al*: 1976; Chan Yeung *et al*: 1978). The occurrence of respiratory disease in grain workers associated with exposure to mites has been reported (Blainey *et al*: 1989).

**Plant allergens:** Common allergens in grain include plant allergens such as pollens (from grasses, weeds, and trees) and storage proteins from damaged grain. Allergy to pollens is common amongst Westernised populations, but its prevalence is lower amongst agricultural workers compared to urban populations (van Hage-Hamsten *et al*: 1987; Iversen and Dahl: 1990). Large concentrations of allergen in grain (e.g., storage proteins) are released by milling processes, and levels of sensitisation amongst millers and bakers are high in comparison to the other grain workers and the general population (Baldo and Wrigley: 1978; Sutton e*t al*: 1984; Prichard *et al*: 1985).

Grain dusts also contains cytotoxic lectins (plant proteins which react with complex sugars on the surface of pathogens) and aqueous extracts of dust from barley, corn, rye, durum wheat, oat, and spring wheat were all found to induce human lymphocyte proliferation in cell culture. However, despite this positive reaction the authors of this study did not demonstrate that lectins were present in all of these grains (Olenchock *et al*: 1986).

**Animal allergens:** Rodent and avian allergens are potent respiratory allergens and are most likely to be encountered during the harvesting or storage of grains on farms. Due to the presence of specific bacteria in avian faecal material, there can be a risk of allergic alveolitis but this is usually associated with farming and not processing of bulk grains (Schenker *et al*: 1998).

**Table 4** summarising the constituents of grain dust, the principle exposures and the diseases associated with these exposures (adapted from Schenker *et al* 1998)

| Respiratory Region | Principal Exposures | Diseases/Syndromes |
|---|---|---|
| **Nose and nasopharynx** | Vegetable dusts | Allergic & non-allergic rhinitis |
| | Aeroallergens | Organic dust toxic syndrome (ODTS) |
| | Mites | |
| | Endotoxins | |
| | Ammonia | |
| **Conducting airways** | | |
| | Vegetable dusts | Bronchitis |
| | Endotoxins | Asthma |
| | Mites | Asthma-like syndrome |
| | Insect antigens | OTDS |
| | Aeroallergens | |
| | Ammonia | |
| | Oxides of nitrogen | |
| | Hydrogen sulfides | |
| **Terminal bronchioles & alveoli** | Vegetable dusts | ODTS |
| | Endotoxins | Pulmonary oedema adult respiratory distress syndrome |
| | Mycotoxins | Bronchiolitis obliterans |
| | Bacteria and fungi | Hypersensitivity pneumonitis |
| | Hydrogen sulfide | Interstitial fibrosis |
| | Oxides of nitrogen | |
| | Paraquat | |
| | Inorganic dusts (silica, silicates) | |

## 4.2 Appendix 2: Summary tables of respiratory disease

**Note:** The results in these tables summarise central estimates of symptom prevalence and do not provide a measure of uncertainty or of numbers in sub-groups for whom changes were greater than indicated by the central estimate. Comparisons between different studies should also be treated with caution since it is probable that different methods and criteria were used to define disease and symptoms over this period of three decades.

**Table 5a)** Cross-sectional studies investigating symptom prevalence and lung function

| DEMOGRAPHICS | | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| Tse KS *et al* (1973) Canada | G: 80 | 47 | 58 | 19 | 50 | 50 | 62 | NA | 43 | 28 | 43 | NA | NA | 18% with FEV<80% predicted | 2 with FVC<80% predicted |
| Kleinfeld M *et al* (1974) USA | G: 55 | 50 | 60 | NA | 27 | NA | NA | 16 | 29 | 33 | NA | NA | NA | 69% (± 1) predicted | 94% (± 2) predicted |
| | BK: 55 | 49 | 60 | NA | 40 | NA | NA | 7 | 20 | 0 | NA | NA | NA | 78% (± 1) predicted | 98% (± 2) predicted |
| Broder I *et al* (1979) Canada | G: 441 | 40 | 53 | 7 | 45 | 28 | 24 | 5 | 14 | 1 | NA | 8 | 11 | 88-97% of predicted | 106-113% of predicted |
| | C: 180 | 42 | 48 | 13 | 27 | 0 | 27 | 6 | 12 | 1 | NA | 8 | 19 | 97-101% of predicted | 113-120% of predicted |
| Gerrard JW *et al* (1979) Canada | G: 60 | 41 | NS | 21 | NA | NA | NA | NA | NA | NA | NA | NA | 15 | 94-103% of predicted | 110% of predicted |
| | C: 30 | 41 | NS | 46 | NA | NA | NA | NA | NA | NA | NA | NA | 20 | 99-103% of predicted | 112% of predicted |
| Becklake *et al* (1980a) Canada | G: 103 | 48 | 67 | NA | 40 | 35 | | 30 | 38 | 25 | NA | NA | NA | 3.2L | 4.0L |
| | C: 39 | 43 | 59 | NA | 13 | 26 | | 13 | 33 | NA | NA | NA | NA | 3.7L | 4.5L |
| Chan Yeng *et al* (1980 Canada | G: 610 | 38 | 49 | 18 | 35 | 34 | | 32 | 30 | 0 | NA | NA | NA | 99% of predicted | 100% of predicted |
| | C: 136 | 44 | 29 | 28 | 23 | 22 | | 25 | 21 | NA | NA | NA | NA | 102% of predicted | 105% of predicted |
| Dosman JA *et al* (1980) Canada | G: 90 | 31 | NS | NA | 11 | NA | NA | 22 | 14 | NA | NA | 23 | NA | NA | NA |
| | C: 90 | 31 | NS | NA | 2 | NA | NA | 10 | 6 | NA | NA | 3 | NA | NA | NA |
| Herbert FA *et al* (1981) Canada | G: 63 | 46 | 36 | 25 | 36 | NA | 38 | 28 | 31 | 14 | NA | NA | NA | 82-97% of predicted | 100-105% of predicted |
| | C: 63 | 47 | 37 | 29 | 32 | NA | 31 | 32 | 12 | NA | NA | NA | NA | 90-110% of predicted | 101-107% of predicted |

**Key to tables:**

**Demographics**

| | | | | |
|---|---|---|---|---|
| AF= Animal feed workers | AT= Atopic | BK= Bakers | BW = Brewery workers | C= Controls |
| EC = external control | G = Grain Workers | GD = Grain docks workers | GF= Grain farmers | GM=Grain millers |
| IC= Internal control | NS= Non-smoker | S = Current smoker | | |

**Symptoms**

| | | | |
|---|---|---|---|
| A = Asthma | B = Breathlessness | Co = Cough | CB= Chronic bronchitis | CT= Chest tightness |
| D = Shortness of breath | NC= nasal congestion | O = Organic dust toxic syndrome | P = Phlegm | W = Wheeze |

**Table 5a continued**: Cross-sectional studies investigating symptom prevalence and lung function

| DEMOGRAPHICS | | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Reference** | **Groups & no** | **Mean Age** | **S (%)** | **AT (%)** | **Co (%)** | **P (%)** | **NC (%)** | **W (%)** | **D (%)** | **O (%)** | **CT (%)** | **CB (%)** | **A (%)** | **FEV1 % or litre capacity** | **FVC % or litre capacity** |
| DoPico GA et al (1984) USA$^Ψ$ | G: 310 | 41 | 49 | NA NA | 65 | 37 | 79 | 59 | 45 | 32 | NA NA | 49 | NA NA | 3.9 L (± 0.9) | 4.9 L (± 0.8) |
| | C: 237 | 41 | 44 | | 42 | 15 | NA | 12 | 30 | NA | | 18 | | 4.1 L (± 0.9) | 5.0 L (± 0.8) |
| Kennedy SM et al (1994) Retired workers study Canada | G: 82 | 69 | 16 | | 16 | 24 | | 21 | 19 | | | | | 79 % (±3) of predicted | 90 % (± 2) of predicted |
| | C: 38 | 67 | 14 | | 16 | 19 | | 14 | 3 | | | | | 88% (±3) of predicted | 98 % (± 2) of predicted |
| Dimich-Ward HD et al (1995) Canada$^Ψ$ | GD: 118 | 44 | 41 | | 18 | 24 | | 27 | 16 | 28 | | | 4 | 101% of predicted | 105% of predicted |
| | G: 555 | 41 | 29 | | 17 | 21 | | 20 | 18 | 14 | | | 7 | 97% of predicted | 102% of predicted |
| | C: 128 | 46 | 10 | | 3 | 3 | | 12 | 9 | | | | 8 | 101% of predicted | 108% of predicted |
| Massin N et al (1995) France | GM: 118 | 38 | 52 | NA NA | 30 | NA NA | 18 | NA NA | 17 | NA NA | NA NA | 13 | 5 | 100% (±15) predicted | 100% (±12) predicted |
| | C: 164 | 38 | 84 | | 24 | | 16 | | 16 | | | 1 | 4 | 100% (±14) predicted | 100%  (±11) predicted |
| Schwartz DA et al (1995) USA$^Ψ$ | G: 410 | 37 | 30 | 26 | 41 | 31 | NA NA | 9 | 14 | NA NA | 14 | NA NA | NA NA | Pre shift = 97.0% (±0.55) predicted Post shift = 1.1% (±0.05) | Pre shift = 93.5% (±0.0.39) predicted Post = 0.8% (±0.05) |
| | C: 201 | 43 | 22 | 23 | 10 | 6 | | 2 | 1 | | 2 | | | Pre = 100% (± 1) predicted Post shift = 1.2% (± 0.2) | Pre shift = 95% (± 1.0) predicted Post shift = 1.0% (± 0.1) |
| Ijadunola K et al (2004) Nigeria$^Ψ$ | GM: 121 | 34 | 4 | | 40 | 56 | 56 | 7 | 14 | | 6 | 6 | | | |
| | IC: 30 | 39 | 13 | | 23 | 20 | 30 | 10 | 10 | | 3 | 3 | | | |
| | EC: 121 | 36 | 2 | | 3 | 5 | 27 | 1 | 5 | | 2 | 2 | | | |

**Key to tables:** (Note: Ψ marks studies demonstrating significant impact of grain exposure on symptoms or lung function)

**Demographics**

| | | | | |
|---|---|---|---|---|
| AF= Animal feed workers | AT= Atopic | BK= Bakers | BW = Brewery workers | C= Controls |
| EC = external control | G = Grain Workers | GD = Grain docks workers | GF= Grain farmers | GM=Grain millers |
| IC= Internal control | NS= Non-smoker | S = Current smoker | | |

**Symptoms**

| | | | | |
|---|---|---|---|---|
| A = Asthma | B = Breathlessness | Co = Cough | CB= Chronic bronchitis | CT= Chest tightness |
| D = Shortness of breath | NC= nasal congestion | O = Organic dust toxic syndrome | P = Phlegm | W = Wheeze |

**Table 5b**) Studies investigating impact of exposure amongst grain farmers on symptom prevalence and lung function

| DEMOGRAPHICS | | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| Warren et al (1980) Canada | GF: 833 | 48 | 25 | NA | 23 | 23 |  | 23 | 12 | 8 | NA | NA | NA | N | |
| Heller et al (1986) UK | GF: 428 | 47 | 35 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | $FEV_1/FEF_{25-75}$ significantly lower in farmers compared to controls | |
|  | C: 356 | 45 | 43 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | | |
| Manfreda J et al (1986) Current vs former farmers Canada | GF: 800 | 41 | 23 | NA | 15 | NA | 15 | 18 | NA | 10 | NA | NA | NA | | |
|  | C: 450 | 51 | 28 | NA | 9 | | 11 | 7 | | 5 | | | | | |
| Blainey AD et al: (1989) UK | GF: 133 | 44 | 34 | 29 | 33% ~one attack of C, W & D | | NA | NA | NA | NA | NA | NA | NA | 105% predicted | 100 % predicted |
| Wilkins et al (1999) USA | GF: 385 | 23-89 | 10 | NA | 9 | 11 | NA | 8 | 16 | NA | NA | NA | NA | NA | NA |
| Sprince NL et al (2000) USA | GF: 384 | 54 | 13 | NA | 11 | 15 | NA | 10 | 21 | NA | NA | 6 | NA | NA | NA |
| Viet SM et al (2001) USA | GF: 98 | 38 | 50 | 47 | 9 | 14 | NA | 25 | 11 | NA | 31 | 4 | 28 | NA | NA |
| Skorska C et al (1998) Poland | GF: 76 | 41 | 64 | NA | 26 | 3 | 6.5 | NA | 20 | NA | 10 | NA | NA | Pre= 81%predicted Post =80% predicted | Pre= 84% predicted Post =82% predicted |
|  | C: 63 | 37 | 26 | NA | 0 | 0 | 0 | NA | 0 | NA | 0 | NA | 0 | Pre= 86% predicted Post =85% predicted | Pre= 89% predicted Post =88% predicted |

**Key to tables:**

**Demographics**

| | | | | |
|---|---|---|---|---|
| AF= Animal feed workers | AT= Atopic | BK= Bakers | BW = Brewery workers | C= Controls |
| EC = external control | G = Grain Workers | GD = Grain docks workers | GF= Grain farmers | GM=Grain millers |
| IC= Internal control | NS= Non-smoker | S = Current smoker | | |

**Symptoms**

| | | | | |
|---|---|---|---|---|
| A = Asthma | B = Breathlessness | Co = Cough | CB= Chronic bronchitis | CT= Chest tightness |
| D = Shortness of breath | NC= nasal congestion | O = Organic dust toxic syndrome | P = Phlegm | W = Wheeze |

**Table 5c**) Studies investigating impact of exposure to grain dust in animal feed workers on symptom prevalence and lung function

| | DEMOGRAPHICS | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| Smid T *et al* (1992) Holland Ψ | AF: 315 | 39 | 57 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 4.1 L (± 0.89) | 5.3 L (± 0.88) |
| | IC: 50 | 39 | 40 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 4.3 L (± 0.74) | 5.5 L (± 0.91) |
| | EC: 125 | 35 | 59 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 3.9 L (± 0.82) | 5.0 L (± 0.92) |
| Baser S *et al* (2003) Turkey Ψ | AF: 108 | 32 | 52 | NA | 12 | 3 | | 5 | 6 | NA | NA | NA | NA | 89% (± 13) predicted | 85 (± 12) predicted |
| | C: 108 | 30 | 46 | NA | 0 | 0 | | 0 | 0 | NA | NA | NA | NA | 99% (± 13) predicted | 92 (± 11) predicted |

**Key to tables:** (Note: Ψ marks studies demonstrating significant impact of exposure on symptoms or lung function)

**Demographics**

| | | | | |
|---|---|---|---|---|
| AF= Animal feed workers | AT= Atopic | BK= Bakers | BW = Brewery workers | C= Controls |
| EC = external control | G = Grain Workers | GD = Grain docks workers | GF= Grain farmers | GM=Grain millers |
| IC= Internal control | NS= Non-smoker | S = Current smoker | | |

**Symptoms**

| | | | | |
|---|---|---|---|---|
| A = Asthma | B = Breathlessness | Co = Cough | CB= Chronic bronchitis | CT= Chest tightness |
| D = Shortness of breath | NC= nasal congestion | O = Organic dust toxic syndrome | P = Phlegm | W = Wheeze |

**Table 5d**) Studies investigating impact of dust from brewery work on symptom prevalence and lung function

| DEMOGRAPHICS | | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| Godnic-Cvar J *et al* (1999) Smoking vs non-smoking Croatia Ψ | BW: 97 | 40 | 52 | NA | 24 | 22 | 36 | NA | 33 | NA | 13 | 22 | 2 | Smokers = 91% predicted Non-smokers = 95% | Smokers = 91% predicted Non-smokers = 90% |
| | C: 76 | 38 | NA | NA | 10 | 8 | 2 | NA | 3 | NA | 0 | 7 | 0 | NA | NA |

**Key to tables:** (Note: Ψ marks studies demonstrating significant impact of grain exposure on symptoms or lung function)

**Demographics**

| | | | | |
|---|---|---|---|---|
| AF= Animal feed workers | AT= Atopic | BK= Bakers | BW = Brewery workers | C= Controls |
| EC = external control | G = Grain Workers | GD = Grain docks workers | GF= Grain farmers | GM=Grain millers |
| IC= Internal control | NS= Non-smoker | S = Current smoker | | |

**Symptoms**

| | | | |
|---|---|---|---|
| A = Asthma | B = Breathlessness | Co = Cough | CB= Chronic bronchitis | CT= Chest tightness |
| D = Shortness of breath | NC= nasal congestion | O = Organic dust toxic syndrome | P = Phlegm | W = Wheeze |

**Table 5e**) Studies investigating impact of smoking on symptom prevalence and lung function

| DEMOGRAPHICS | | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| DoPico GA *et al* (1977) USA | G: 300 | 39 | 59 | 28 | 76 | 62 | 64 | 42 | 45 | 19 | 49 | 37 | 2.3 | 3.9 L (±0.80) | 4.9 L (± 0.8) |
| Patel KR *et al* (1981) Smoking vs non-smoking UK | G: 75 | 48 | 63 | 25 | S=~33 | NA | NA | S=~50 | S=~35 | NS | NA | NA | NA | S = 82% predicted | S = 90% predicted |
| | | | | | NS=~13 | NA | NA | NS=~21 | NS=~16 | | NA | NA | NA | NS = 90% predicted | NS = 90% predicted |
| | C 48 | 52 | 31 | NA | NA | NA | NA | NA | NA | NS | NA | NA | NA | S = 79% predicted | S = 84% predicted |
| | | | | | | | | | | | | | | NS = 95% predicted | NS = 92% predicted |
| Cotton DJ *et al* (1982) Smoking vs non-smoking Canada Ψ | G: 82 | 23 | 100 | NA | 22 | NA | NA | 32 | 11 | NA | NA | NA | 4 | 109% (± 14) of predicted | 115% (± 14) of predicted |
| | G: 82 | 23 | 0 | NA | 0 | NA | NA | 13 | 6 | NA | NA | NA | 0 | 110% (± 14) of predicted | 113% (± 13) of predicted |
| | C: 82 | 23 | 100 | NA | 15 | NA | NA | 33 | 15 | NA | NA | NA | 0 | 109% (± 14) of predicted | 114% (± 14) of predicted |
| | C: 82 | 23 | 0 | NA | 1 | NA | NA | 7 | 1 | NA | NA | NA | 6 | 112% (± 13) of predicted | 114% (± 11) of predicted |
| Cotton DJ *et al* (1983) Smoking vs non-smoking Canada | G: 195 smoker | 31 | 100 | | 25 | | | 31 | 13 | | | 20 | 3 | 109% (± 13) of predicted | |
| | G: 195 non-smoker | 31 | 0 | | 18 | | | 27 | 10 | | | 18 | 0 | | |
| | C: 195 smoker | 31 | 100 | | 10 | | | 17 | 20 | | | 7 | 3 | 110% (± 15) of predicted | |
| | C: 195 non-smoker | 31 | 0 | | 4 | | | 14 | 9 | | | 7 | 6 | | |

**Key to tables:** (Note: Ψ marks studies demonstrating significant impact of grain exposure on symptoms or lung function)

**Demographics**

| | | | | |
|---|---|---|---|---|
| AF= Animal feed workers | AT= Atopic | BK= Bakers | BW = Brewery workers | C= Controls |
| EC = external control | G = Grain Workers | GD = Grain docks workers | GF= Grain farmers | GM=Grain millers |
| IC= Internal control | NS= Non-smoker | S = Current smoker | | |

**Symptoms**

| | | | | |
|---|---|---|---|---|
| A = Asthma | B = Breathlessness | Co = Cough | CB= Chronic bronchitis | CT= Chest tightness |
| D = Shortness of breath | NC= nasal congestion | O = Organic dust toxic syndrome | P = Phlegm | W = Wheeze |

**Table 5f)** Studies investigating level of dust exposure & exposure duration on symptom prevalence and lung function

| DEMOGRAPHICS | | | | SYMPTOMS | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Groups & no | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| Huy T *et al* (1991) Canada $\Psi$ | G: 123 Dust <4mg/m$^3$ | 41 | 29 | | 5 | 15 | | 7 | 11 | | | | 4 | 4.0 L (± 0.3) | 5.0 L (± 0.4) |
| | G: 276 Dust <4-9mg/m$^3$ | 42 | 36 | | 8 | 16 | | 10 | 13 | | | | 7 | 3.9 L (± 0.3) | 4.9 L (± 0.4) |
| | G: 20 Dust >9mg/m$^3$ | 55 | 25 | | 11 | 23 | | 23 | 21 | | | | 5 | 3.7 L (± 0.3) | 4.6 L (± 0.4) |
| | C: 55 | 52 | 9 | | 6 | 4 | | 14 | 7 | | | | 9 | 4.2 L (± 0.3) | 5.2 L (± 0.4) |
| Bachman M *et al* (1991) South Africa $\Psi$ | GM: 32 Never smoker | 43 | 67 | 0 | 19 | 28 | 22 | 16 | 16 | | 28 | | 0 | >5% FEV1 decrease Mon-Thu = 16% | |
| | GM: 43 Ex-smoker | | | 7 | 23 | 14 | 16 | 28 | 16 | | 12 | | 5 | >5% FEV1 decrease Mon- Thu = 11% | |
| | GM: 149 Current smoker | | | 2 | 29 | 34 | 20 | 38 | 22 | | 26 | | 10 | >5% FEV1 decrease Mon-Thu= 7% | |
| | GM: 29 Low dust | | | 0 | 14 | 10 | 10 | 24 | 14 | | 21 | | 7 | >5% FEV1 decrease Mon-Thu = 10% | |
| | GM: 149 Medium dust | | | 5 | 29 | 29 | 15 | 33 | 18 | | 21 | | 6 | >5% FEV1 decrease Mon-Thu = 8% | |
| | GM: 44 High dust | | | 0 | 23 | 36 | 36 | 34 | 25 | | 32 | | 9 | >5% FEV1 decrease Mon- Thu = 8% | |

**Key to tables:** (Note: $\Psi$ marks demonstrating significant impact of grain exposure on symptoms or lung function)

**Demographics**

AF= Animal feed workers    AT= Atopic    BK= Bakers    BW = Brewery workers    C= Controls
EC = external control    G = Grain Workers    GD = Grain docks workers    GF= Grain farmers    GM=Grain millers
IC= Internal control    NS= Non-smoker    S = Current smoker

**Symptoms**

A = Asthma    B = Breathlessness    Co = Cough    CB= Chronic bronchitis    CT= Chest tightness
D = Shortness of breath    NC= nasal congestion    O = Organic dust toxic syndrome    P = Phlegm    W = Wheeze

**Table 5f continued)** Studies investigating level of dust exposure & exposure duration on symptom prevalence and lung function

| DEMOGRAPHICS | | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| Fonn S *et al* (1993) South Africa Ψ | GM: 38 Low dust ~2 mg/m$^3$ | 39 | 62 | 12 | 40 | 36 | 21 | 25 | 8 | | 28 | 11 | | FEV1 decrease (Mon-Fri) 3.0 to 3.3 L (+0.10) | FVC decrease (Mon-Fri) 3.8 to 4.1 L (+0.3) |
| | GM: 38 Medium ~4 mg/m$^3$ | 36 | 61 | 3 | 60 | 55 | 36 | 30 | 12 | | 33 | 3 | | FEV1 decrease (Mon-Fri) 3.3 to 3.4 (+0.10) | FVC decrease (Mon-Fri) 4.1 to 4.2 L (+0.1) |
| | GM: 38 High dust ~ 6 mg/m$^3$ | 36 | 60 | 8 | 42 | 45 | 42 | 33 | 10 | | 39 | 15 | | FEV1 decrease (Mon-Fri) 3.4 to 3.4 L (+0.1) | FVC decrease (Mon-Fri) 4.3 to 4.3 L (-0.1) |
| | GM: 38 Very high dust~19mg/m$^3$ | 38 | 63 | 13 | 47 | 57 | 63 | 37 | 10 | | 40 | 23 | | FEV1 decrease (Mon-Fri) 3.4 to 3.4 L (+0.00) | FVC decrease (Mon-Fri) 4.2 to 4.2 L (-0.1) |
| Peelen SJ *et al* (1996) Holland Ψ | AF: 393 | 40 | 49 | | 8 | 4 | | 5 | 5 | | NA NA | NA | NA | 102% (± 15) predicted | 102% (± 15) predicted |
| | G: 438 | 42 | 52 | | 11 | 10 | | 12 | 10 | | NA NA | | | 104% (± 14) predicted | 104% (± 14) predicted |

**Key to tables:** (Note: Ψ marks demonstrating significant impact of grain exposure on symptoms or lung function)

**Demographics**

| | | | | |
|---|---|---|---|---|
| AF= Animal feed workers | AT= Atopic | BK= Bakers | BW = Brewery workers | C= Controls |
| EC = external control | G = Grain Workers | GD = Grain docks workers | GF= Grain farmers | GM=Grain millers |
| IC= Internal control | NS= Non-smoker | S = Current smoker | | |

**Symptoms**

| | | | | |
|---|---|---|---|---|
| A = Asthma | B = Breathlessness | Co = Cough | CB= Chronic bronchitis | CT= Chest tightness |
| D = Shortness of breath | NC= nasal congestion | O = Organic dust toxic syndrome | P = Phlegm | W = Wheeze |

**Table 5g)** Studies specifically investigating work shift effect on symptom prevalence and lung function

| DEMOGRAPHICS | | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| Awad MA *et al* (1981) Sudan | GM: 100 | 34 | 34 | NA | 26 | 29 | 19 | NA | NA | NA | 22 | 29 | 18 | Before shift: 3.2 L (± 0.8) End of shift: 3.0 L (± 0.8) | Before shift: 3.9 L (± 0.8) End of shift: 3.6 L (± 0.7) |
| | C: 30 | 35 | 40 | NA | 7 | 7 | 3 | NA | NA | NA | 3 | 7 | 3 | Before shift: 3.7 L (± 0.6) End of shift: 3.6 L (± 0.6) | Before shift: 4.5 L (± 0.7) End of shift: 4.4L (± 0.6) |
| DoPico GA *et al* (1983) USA [Ψ] | G: 248 | 41 | 48 | 13 | 48 | 37 | 38 | 12 | 12 | 4 | NA | NA | NA | Pre shift= 3.5 (± 0.8) L Post shift = 3.5 (± 0.9) L | Pre shift = 4.7 L (± 0.9) Post shift = 4.7 L (± 0.9) |
| | C: 192 | 41 | 45 | 21 | 32 | 18 | 25 | 8 | 5 | 2 | NA | NA | NA | Pre shift = 3.9 L (± 0.8) Post shift = 3.9 L (± 0.7) | Pre shift = 4.8 L (± 0.8) Post shift = 4.8 L (± 0.7) |
| Yach D *et al* (1985) South. Africa [Ψ] | GM: 582 | 37 | 68 | 22 | 46 | 35 | 25 | 24 | 25 | NA | 23 | NA | NA | Start week: 2.6 L (± 0.4) End week: 2.6 L (± 0.6) | Start week 3.8 L (±0.7) End week: 3.8 L (±0.7) |
| | C: 153 | 36 | 68 | 18 | 30 | 17 | 14 | 10 | 20 | NA | 17 | NA | NA | Start week: 2.6 L (± 0.7) End week: 2.7 L (± 0.7) | Start week: 3.9 L (±0.9) End week: 4.0 L (±0.8) |
| Gimenez C *et al* (1995) France [Ψ] | GM: 142 | 42 | 63 | 12 | 15 | 13 | NA | 18 | 24 | NA | 8.5 | | 4 | Pre = 100% predicted Post = 99% predicted | Pre = 101% predicted Post= 99% predicted |
| | C: 37 | 42 | 13 | 16 | 0 | 0 | NA | 8 | 16 | | 0 | | 3 | Pre= 103% predicted Post = 99% predicted | Pre = 104% predicted Post = 99% predicted |
| Blaski CA *et al* (1996) USA | G: 172 | 40 | 26 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | Pre = 96 % (± 1) predicted Post shift = -0.1% (± 0.2) | NA |
| | C: 78 | 43 | 17 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | Pre = 98% (± 0.2) predicted Post shift = 1.4% (±0.5) | NA |

**Key to tables:** (Note: Ψ marks studies demonstrating significant impact of grain exposure on symptoms or lung function)

**Demographics**

| | | | | |
|---|---|---|---|---|
| AF= Animal feed workers | AT= Atopic | BK= Bakers | BW = Brewery workers | C= Controls |
| EC = external control | G = Grain Workers | GD = Grain docks workers | GF= Grain farmers | GM=Grain millers |
| IC= Internal control | NS= Non-smoker | S = Current smoker | | |

**Symptoms**

| | | | | |
|---|---|---|---|---|
| A = Asthma | B = Breathlessness | Co = Cough | CB= Chronic bronchitis | CT= Chest tightness |
| D = Shortness of breath | NC= nasal congestion | O = Organic dust toxic syndrome | P = Phlegm | W = Wheeze |

**Table 5h)** Longitudinal studies investigating symptom prevalence & lung function data

| DEMOGRAPHICS | | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| Broder I *et al* (1984) Newly hired grain workers. Examined at baseline & + 3months employment Long term employed (~9yrs) grain workers Examined at baseline and 3 months later Canada $^\Psi$ | G: 27  Baseline | 24 | 59 | | 15 | 11 | 7 | | | | | | | 104% (± 14) of predicted | 106% (± 14) of predicted |
| | G: 27 + 3 months | 24 | 63 | | 52 | 33 | 19 | | | | | | | 107% (± 12) of predicted | 104% (± 12) of predicted |
| | C: 14  Baseline | 21 | 14 | | 14 | 7 | 43 | | | | | | | 104% (± 10) of predicted | 101% (± 8) of predicted |
| | C: 14  + 3 months | 21 | 14 | | 14 | 7 | 36 | | | | | | | 101% (± 10) of predicted | 101% (± 5) of predicted |
| | G: 31 (9yrs) Baseline | 32 | 48 | | 53 | 40 | 40 | | | | | | | 113% (± 15) of predicted | 106% (± 12) of predicted |
| | G: 31 (9yrs) + 3 months | 32 | 55 | | 43 | 37 | 37 | | | | | | | 109% (± 14) of predicted | 103% (± 12) of predicted |
| | C: 13 (9yrs) Baseline | 34 | 77 | | 54 | 54 | 23 | | | | | | | 110% (± 13) of predicted | 108% (± 12) of predicted |
| | C: 13 (9yrs)+ 3 months | 34 | 92 | | 38 | 38 | 23 | | | | | | | 108% (± 13) of predicted | 108% (± 12) of predicted |
| James *et al* (1990) Australia | G: 41 baseline | 27 | 62 | 22 | 32 | 42 | NA NA | 22 | 7 | NA NA NA NA | 12 | NA NA NA NA | NA | 95% (± 12) predicted | 99% (± 12) predicted |
| | G: 41 & 2 weeks exposure | | | | 56 | 54 | | 31 | 23 | | 28 | | | | |
| | C: 10 baseline | 50 | 20 | 50 | 50 | 50 | | 30 | 40 | | 50 | | | 100% (± 13) predicted | 99% (±17) predicted |
| | C: 10 & 2 weeks | | | | 20 | 20 | | 10 | 0 | | 0 | | | | |
| Post W *et al* (1998) Holland $^\Psi$ | G: 320 (1987) | 42 | 60 | NA | NA | NA | | 16 | NA | | 4 | | NA | Pre –post (1987-1992) Low = -36 ml.s$^{-1}$ Middle = -49 ml.s$^{-1}$ High = -58 ml.s$^{-1}$ | Pre –post (1987-1992) Low = -41 ml.s$^{-1}$ Middle = -58ml.s$^{-1}$ High = -52 ml.s$^{-1}$ |
| | G: 144 (1992) | 38 | 53 | NA | 4 | 1 | | 2 | NA | | 4 | 7 | 6 | | |

**Key to tables:** (Note: $\Psi$ marks demonstrating significant impact of grain exposure on symptoms or lung function)

**Demographics**

| | | | | |
|---|---|---|---|---|
| AF= Animal feed workers | AT= Atopic | BK= Bakers | BW = Brewery workers | C= Controls |
| EC = external control | G = Grain Workers | GD = Grain docks workers | GF= Grain farmers | GM=Grain millers |
| IC= Internal control | NS= Non-smoker | S = Current smoker | | |

**Symptoms**

| | | | | |
|---|---|---|---|---|
| A = Asthma | B = Breathlessness | Co = Cough | CB= Chronic bronchitis | CT= Chest tightness |
| D = Shortness of breath | NC= nasal congestion | O = Organic dust toxic syndrome | P = Phlegm | W = Wheeze |

**Table 5h continued)** Canadian 12 year longitudinal and intervention study investigating symptom prevalence & lung function

| | DEMOGRAPHICS | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| Pahwa P *et al* (2003) & Pahwa P *et al* (2006) 12 yrs with reduction of average dust exposure from Cycle 3 Canada[Ψ] | **G: 5702 Cycle 1(1978-81)** | 35 | 51 | | 29 | 27 | | 29 | 29 | | | | | | | |
| | Non-smokers | | | | | | | | | | | | | 4.25 (± 0.7) | 5.32 (± 0.8) |
| | Ex-smokers | | | | | | | | | | | | | 3.79 (± 0.8) | 5.09 (± 1.0) |
| | Current-smokers | | | | | | | | | | | | | 4.02 (± 0.8) | 5.21 (± 0.9) |
| | **G: 5488 Cycle 2 (1981-84)** | 36 | 46 | | 32 | 30 | | 29 | 29 | | | | | | | |
| | Cycle 2 Non-smokers | | | | | | | | | | | | | 4.38 (± 0.7) | 5.43 (± 0.8) |
| | Cycle 2 Ex-smokers | | | | | | | | | | | | | 4.03 (± 0.8) | 5.27 (± 0.8) |
| | Cycle 2 Current-smokers | | | | | | | | | | | | | 4.17 (± 0.7) | 5.38 (± 0.8) |
| | **G: 3713 Cycle 3 (1984-87)** | 37 | 40 | | 16 | 18 | | 22 | 17 | | | | | | | |
| | Cycle 3 Non-smokers | | | | | | | | | | | | | 4.25 (± 0.6) | 5.27 (± 0.8) |
| | Cycle 3 Ex-smokers | | | | | | | | | | | | | 3.81 (± 0.8) | 4.96 (± 0.8) |
| | Cycle 3 Current-smokers | | | | | | | | | | | | | 3.96 (± 0.7) | 5.10 (± 0.8) |
| | **G: 2832 Cycle 4 (1987-90)** | 38 | 39 | | 13 | 13 | | 10 | 13 | | | | | | | |
| | Cycle 4 Non-smokers | | | | | | | | | | | | | 4.40 (± 0.7) | 5.44 (± 0.8) |
| | Cycle 4 Ex-smokers | | | | | | | | | | | | | 4.07 (± 0.8) | 5.22 (± 0.9) |
| | Cycle 4 Current-smokers | | | | | | | | | | | | | 4.13 (± 0.7) | 5.30 (± 0.8) |
| | **G: 3072 Cycle 5 (1990-93)** | 38 | 34 | | 11 | 12 | | 11 | 11 | | | | | | | |
| | Cycle 5 Non-smokers | | | | | | | | | | | | | 4.42 (± 0.7) | 5.46 (± 0.8) |
| | Cycle 5 Ex-smokers | | | | | | | | | | | | | 4.10 (± 0.8) | 5.17(± 0.8) |
| | Cycle 5 Current-smokers | | | | | | | | | | | | | 4.20 (± 0.7) | 5.36 (± 0.8) |
| Senthilselvan A et *al*: 2010 Canada[Ψ] | **GF** Baseline 1990/1991 | 44.6 | 36.8 | | | | | | | | | | | 107 (± 12.0) predicted | 105 (±13.7) predicted |
| | **C:** Baseline 1990/1991 | 40.7 | 57.5 | | | | | | | | | | | 104.5 (± 11.9) predicted | 103.0 (±13.1) predicted |
| | **GF** Baseline 1994/1994 | 48.3 | 49.1 | | | | | | | | | | | 104.8 (± 12.5) predicted | 100.4 (±13.7) predicted |
| | **C:** Baseline 1994/1995 | 46.2 | 70.0 | | | | | | | | | | | 106.2 (±12.2) predicted | 101.5 (±13.7) predicted |

**Table 5h continued) Canadian 12 year longitudinal and intervention study investigating symptom prevalence & lung function**

| DEMOGRAPHICS | | | | | SYMPTOMS | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Groups & no | Mean Age | S (%) | AT (%) | Co (%) | P (%) | NC (%) | W (%) | D (%) | O (%) | CT (%) | CB (%) | A (%) | FEV1 % or litre capacity | FVC % or litre capacity |
| | **GF** Baseline 2003/2004 | 56.0 | 47.2 | | | | | | | | | | | 99.1 (±14.1) predicted | 93.5 (±15.7) predicted |
| | **C:** Baseline 2003/2004 | 54.0 | 59.7 | | | | | | | | | | | 101.7 (±13.6) predicted | 95.3 (±14.0) predicted |
| Dimich-Ward H, *et al* (2011): Respiratory health changes in 2 cohorts of terminal grain elevator workers Studied 30 years apart Canada Ψ | **GD:** 584 workers from the 1978 | 38.4 | 25.5 | 13.4 | 26.6 | 30.7 | | 20.9 | 25.2 | | | | 1.9 | 86.2 (± 4.0) | 92.1 (± 3.5) |
| | **GD:** 215 workers from 2008 survey. | 45.7 | 46.0 | 51.2 | 8.8 | 14.0 | | 14.4 | 7.4 | | | | 4.2 | 92.5 (± 3.0) | 102.3 (± 2.0) |
| | **GD:** 59 workers who took part in 1978 | 25.3 | 36.2 | 13.8 | | | | | | | | | | Decrement in FEV1 of 29.9 (±13.7 ml) year | Decrement in FVC of 23.5 (±17.0 ml) year |
| | **GD:** 59 workers who took part in 2008 | 55.3 | 10.3 | 19.0 | | | | | | | | | | | |
| Karunanayake CP *et al*: 2011 Cohort study of grain farmers Canada Ψ | **GD**: Baseline in 1993 (n=871) Males 41%<br>**GD:** Baseline in 1993 Females 59% | 46.8 | 46.1 | | 16.1 | 18.1 | | 25.5 | | | | | | | |
| | **GD:** Follow-up in 2003 (n=871) Males 41%<br>**GD**: Follow-up in 2003 (n=871) Females 59% | ~66.0 | 47.9 | | 19.6 | 21.4 | | 30.1 | | | | | | | |

**Key to tables:** (Note: Ψ marks studies demonstrating significant impact of grain exposure on symptoms or lung function)

**Demographics**

| | | | | |
|---|---|---|---|---|
| AF= Animal feed workers | AT= Atopic | BK= Bakers | BW = Brewery workers | C= Controls |
| EC = external control | G = Grain Workers | GD = Grain docks workers | GF= Grain farmers | GM=Grain millers |
| IC= Internal control | NS= Non-smoker | S = Current smoker | | |

**Symptoms**

| | | | | |
|---|---|---|---|---|
| A = Asthma | B = Breathlessness | Co = Cough | CB= Chronic bronchitis | CT= Chest tightness |
| D = Shortness of breath | NC= nasal congestion | O = Organic dust toxic syndrome | P = Phlegm | W = Wheeze |

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# Risks to respiratory health in the grain industry

A detailed literature search was carried out to summarise evidence about respiratory disease caused by exposure to grain dust. Long term epidemiological studies examining the risk for respiratory disease in grain workers were undertaken in Canada and the USA from the 1970s to the late 1990s. Smaller studies were undertaken in the UK and Europe but mostly focussed on respiratory disease in arable and livestock farmers.

The conclusion of this review is that the damaging effects of grain dust on the respiratory tract are accumulative and occur at high concentrations of exposure. Acute responses also occur and include declines in lung function as well as irritation and inflammation of the airways. There is less evidence that grain dust exposure causes occupational asthma despite the dusts containing allergens. This may be due to a 'healthy worker' effect with those already having, or developing, asthma leaving employment earlier than others. There is stronger evidence that the long term effects of exposure include emphysema, chronic obstructive pulmonary disease and interstitial fibrosis of the lung. The risk of developing extrinsic allergic alveolitis has reduced through preventing damp conditions in stored grain.

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