Asthma at work

Part 1: nature, extent and causes of occupational and work-related asthma

In the first of a series of articles on work-related asthma, David Fishwick and Nicholas Warren from the HSE's Health and Safety Laboratory explore the scale of the problem and the leading causes of this important class of occupational illnesses.

ASTHMA is a common condition in working-age adults, an important proportion of which is either caused, or aggravated, by exposures in the workplace. This introductory article is the first in a series that will deal with various aspects of work-related and occupational asthma. Future articles will cover the diagnosis, occupational management and prevention of the conditions, including occupational hygiene considerations, health surveillance requirements and other legal duties.

TERMINOLOGY

Work-related asthma is a general term that includes both *occupational asthma* and *work-aggravated asthma*. These are important diagnoses to consider in workers whose asthma symptoms (for example wheezing, chest tightness) or asthma control (eg peak flow readings, medication requirements) worsens or escalates at work or improves on rest days. Figure 1 (p.28), adapted from an expert consensus[1], illustrates working definitions for, and the relationship between, these terms, which are also explained below.

Occupational asthma

There is no universally accepted definition of occupational asthma. Occupational asthma can be thought of as asthma that is either caused by inhaled agents at work when development of an allergy (or sensitisation) to an inhaled workplace agent is thought to be responsible (occupational asthma due to sensitisation), or alternately asthma that is caused by exposure to inhaled irritants at work (acute irritant-induced asthma).

Occupational asthma due to sensitisation normally develops after a period of exposure to the causative agent, the so-called latent period. This period of exposure is normally at least a few months in duration, but can be up to a number of years[2,3]. During this time, sensitisation develops, leading to the development of asthma. Rhinitis is a relatively common accompaniment in this situation, particularly when workers are exposed to high molecular weight agents, and should always be enquired about specifically.

How this allergy develops is better understood for certain exposures – such as high molecular weight agents such as flour, and laboratory animal proteins – than for others, including exposure to low molecular weight agents such as paints containing isocyanates, epoxy-based resins and wood dust. For example, in bakery workers exposed to flour dust and enzymes a number of cross-sectional and longitudinal studies[4,5,6] have found evidence of a dose-response relationship between both levels and duration of exposure and the development of immunological sensitisation and work-related respiratory symptoms. Whilst such epidemiological studies have in the main been based on estimates of average exposure levels over the working day, short-term peak exposures may play an important role in the development of occupational sensitisation more broadly[7].

Given that occupational asthma has a recognised cause; it should be almost entirely preventable[8]. It is important to identify workers with asthma caused by work because: their outcome is generally better if a cause is identified[9]; established cases are associated with very significant personal[10,11] and wider[12] costs (estimated at between £100,000 and £200,000 lifetime costs to society per case, at 2003 prices); and there is UK-based evidence to suggest that the diagnosis of occupational asthma may be missed[13] or delayed[14].

Acute irritant-induced asthma is most often included as a subtype of occupational asthma. Most experts agree that a very high dose of an inhaled 'irritant' exposure at work can also cause asthma. This is termed acute irritant-induced asthma. There is evidence, for example, that asthma has been caused by high exposures to irritant chemicals (for example methyl isothiocyanate following a railway accidental spill[15]), acids[16] and complex mixtures of alkaline dust and combustion products[17] (as seen after the collapse of New York's World Trade Center in 2001). The role of multiple lower and or continuous exposures to irritants in causing asthma remains less clear, and is actively debated[18].

Work-aggravated asthma

Work-aggravated asthma is a term used to describe workers who complain that their symptoms are worse

Box 1: population attributable fractions

The fraction of cases in a population that occur because of a certain exposure is called the population attributable fraction (PAF). These figures are often used to estimate the burden of a particular disease (in this case asthma) that can be attributed to a given exposure (in this case occupational exposure). They are normally written as percentages, and generally calculated from results of epidemiological studies. In the case of occupational asthma, PAF values reflect the fraction of disease that would theoretically be avoided should all relevant occupational exposures cease.

For this interpretation to be correct, the exposure needs to be causally related to the outcome, rather than being merely associated with the disease. While PAF estimates are a useful guide to how much asthma is caused by occupational exposures, they also have their limitations. For example, they should not be used to identify individual risks of developing occupational asthma in each worker, and – given the inherent uncertainties in their estimation – they should only be used as a guide to the number of cases that might occur.

Many studies contributed to the American Thoracic Society consensus statement about the occupational contribution to airways diseases[22]. Twenty-one studies were included, and a median PAF of 15% was identified as the fraction of all asthma that is attributable to workplace exposures. Given different geographies and study designs, the range of PAFs in this consensus was large, from 4% to 58%. Similarly, the UK 1958 Birth Cohort Study identified a PAF of 16% for occupational contribution to asthma[32].

when they are at work, when occupational asthma has been excluded. A variety of causes is described, but not limited to *inhaled* exposures[19]. For example, workers with asthma may identify changes in workplace temperature, or work-related stress, as aggravants of their asthma. Just as with occupational asthma, work-aggravated asthma is also known to be associated with a variety of adverse personal and wider impacts[20].

SCALE OF THE PROBLEM

Accurate data relating to the incidence of occupational asthma are remarkably scarce, which is due both to the difficulty of identifying all cases, and also that the sizes of the working populations that cases are drawn from are often hard to quantify. Nonetheless, international population-based studies suggests that one in six adult-onset asthma cases can be attributed to workplace exposures[21] , and that approximately 15% of the total burden of asthma relates to harmful workplace exposures[22]. The 15% figure is an example of a population attributable fraction (PAF). See box 1 above for details.

Despite this relatively large PAF, the numbers of actual cases of occupational asthma captured by reporting schemes remain relatively low. For example, the most recent Health and Safety Executive (HSE) statistics indicate that between 200 and 300 cases of new work-related asthma are reported by respiratory physicians each year, with no recent important change, year on year, over the past decade. It is likely, however, that these figures represent a significant underestimate of the scale of the problem[23]. The Labour Force Survey, for example, estimates that there are around 18,000 new cases of self-reported 'breathing or lung problems' caused or made worse by work every year.

Similarly, a relatively recent large European epidemiological study[24] estimated an incidence of work-related asthma of 25 to 30 cases per 100,000 person years (equivalent to 7,500 to 9,000 new cases a year). The incidence of occupational asthma in specific exposed populations is often considerably higher: the incidence of occupational asthma in motor vehicle repair workers exposed to isocyanate-containing paints was reported in one study to be in excess of 79 cases per 100,000 person years[25], whilst an even higher incidence of 900 cases per 100,000 person-years has been reported for toluene diisocyanate (TDI) production workers[26].

There are understandably few data on the size of the problem posed specifically by acute irritant-induced asthma, given the general accidental nature of the exposure. In 2016, an estimated 46 cases of either irritant asthma or inhalation accident were referred to the Surveillance of Work-related and Occupational Respiratory Disease (SWORD) scheme. This figure is again likely to be an underestimate. Specific industry studies have also estimated incidence of irritant gas related disease[27]. Ozone and other irritant gas exposed workers were identified in one study to have an incidence of exposure-related asthma of 1,920 cases per 100,000 person-years.

Work aggravated asthma is also common. A review by the American Thoracic Society estimated that around one in five working adults with asthma complained of asthma symptoms that were worse at work[28]. One study only has been carried out in the UK, and shows that approximately one in three working adults with asthma complained of such symptoms[20].

Commonly recognised causes

Between 300 and 400 causes of occupational asthma have been described. The top five implicated exposures in the UK are currently isocyanates (chemicals predominantly seen in activated paints), flour, cleaning agents, wood dusts and enzymes/amylase[29]. Box 2 summarises the common causes of occupational asthma more comprehensively, combining a number of sources including recent SWORD scheme[30] data and the UK Standard of Care for occupational asthma[31] .

Recent findings from the UK 1958 Birth Cohort Study[32] identified similar jobs and exposures. Adult-onset asthma was associated with farmers, hairdressers, printing workers and seven occupations

where cleaning agents were used. When a job exposure matrix was used to ascribe likely exposures to workers based on their job titles, adult-onset asthma was associated with five of the 18 high-risk specific exposures. These were flour, enzymes, cleaning/disinfecting products, metal and metal fumes, and textiles.

Novel causes

Although it is accepted that the majority of reported cases of occupational asthma concern people who work in jobs where they are exposed to agents that are known to be associated with the condition, various interesting and novel causes have also been identified[33].

Soybeans are a species of legume that have become one of the most widely eaten global foodstuffs. There is evidence that US soybean process workers[34] have an increased risk of asthma as a likely consequence of their exposure to this allergen, and work from South African process workers[35] has identified allergy to soybean as a predictor of allergic rhinitis. Interestingly, soybean exposure was also thought to be responsible for an epidemic of asthma in Barcelona, which was attributed to environmental exposures to soybean allergen following their offloading in the Barcelona docks. Once the cause was realised and remedied, those affected with asthma appeared to have a more favourable prognosis[36].

A UK outbreak of occupational asthma was described in a group of detergent workers, working with various enzymes[37] (including amylase, protease and cellulose). About one-quarter of workers had a positive skin-prick test to at least one detergent enzyme, and the study team identified a very significant number of workers who had developed occupational asthma. Interestingly, age, gender and smoking were not associated with any health outcomes associated with detergent exposure.

Other novel and recently reported causes of occupational asthma include occupational exposure to coffee beans. Occupational asthma was described in a 43-year-old man exposed to coffee beans contaminated with a powder containing the fungus *Chrysonilia sitophila*[38]. The diagnosis was confirmed with serial peak expiratory flow (PEF) recordings, an immediate asthma response following a workplace challenge and the presence of specific IgE to this allergen. Occupational asthma has also been described from exposures to *Plantago ovata* seed, during laxative preparation, in healthcare workers[39], artemia (brine shrimp) fish fry feed in aquaculture[40] and gum arabic, a mix of glycoproteins and polysaccharides, used in the food industry[41]. Occupational allergy has also been described in New Zealand green-lipped mussels process workers[42].

The diverse nature of these cases should also remind clinicians seeing asthma patients to be vigilant of potentially new causes of occupational asthma, and not to exclude the diagnosis based on the absence of a typical known cause at work.

Box 2: a selection of commonly reported jobs, tasks and exposures associated with occupational asthma

Occupations: animal handlers; assemblers, assemblers (electrical products), assemblers (vehicles and metal goods); bakers, flour confectioners, pastry makers; carpenters and joiners; chemical workers; cleaners, domestics; cooks; detergent workers; electrical and electronics workers; farm workers; fish and seafood processors; foam manufacturers; food, drink and tobacco process workers; forestry workers; hairdressers; metal machining setters and workers, metal working machine workers, metal working production and maintenance fitters; nurses and other health professionals; plastic and rubber workers; production workers and maintenance managers; scientific researchers; textile workers; vehicle spray painters and mechanics; welders; and wood workers.

Specific exposures: adhesives; aldehydes; animal dander and proteins; biological enzymes; certain chemicals including hairdressing products; cleaning agents; colophony and solder fluxes; detergents; flour; foodstuffs; grain; isocyanates; latex; metals; metal working fluids; plastics; resins; rubbers; sea foods; textile dusts; welding fumes; and wood dust.

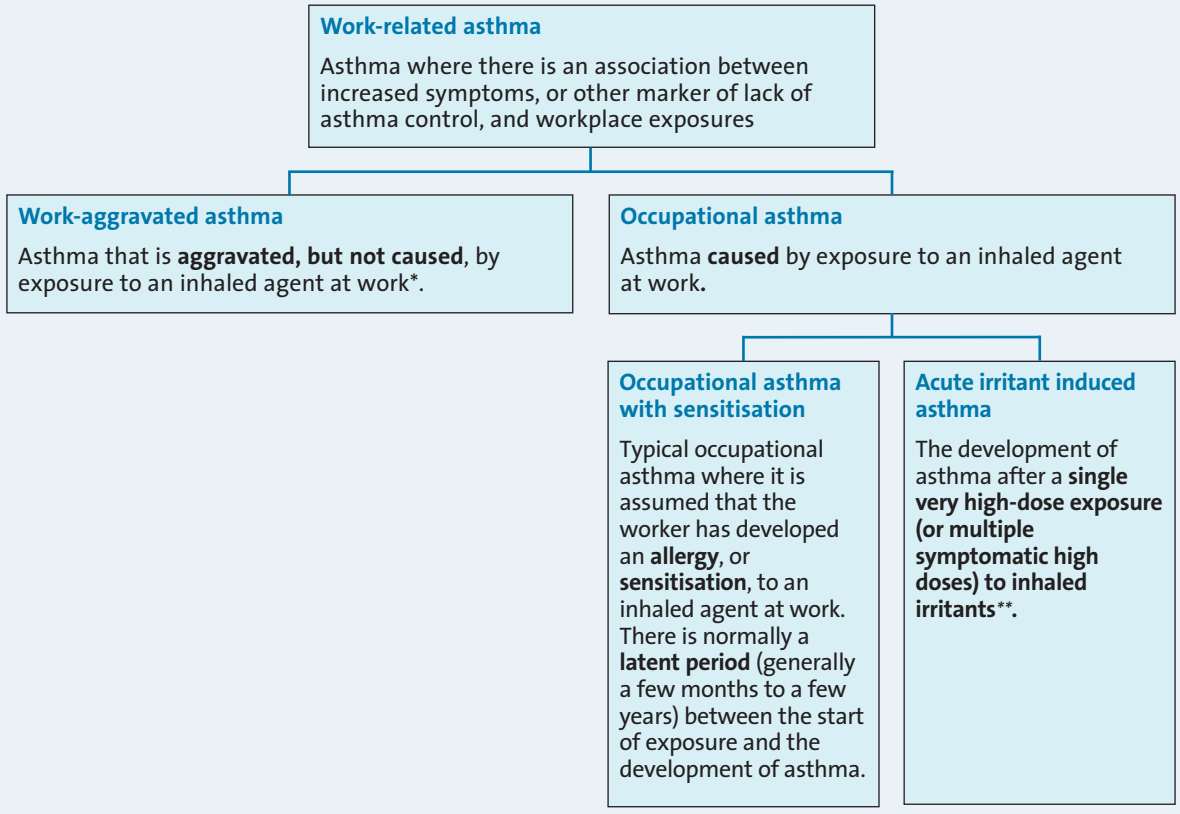
Other risk factors (non-occupational exposures)

Whilst exposure to a known cause of asthma appears to be the predominant risk factor, it is clear, at least from SWORD and THOR data, that occupational asthma occurs over a wide range of ages, and that there is little difference by gender. Other potential risks have been extensively reviewed; given that only a small proportion of exposed workers go on to develop occupational asthma. One comprehensive review[43] identified various non-exposure-related risks for developing occupational asthma.

The presence of atopy, or an allergic 'predisposition', appears to be a risk factor for asthma that is caused by high molecular weight agents, such as flour and animal proteins, with studies suggesting an approximate doubling of the risk of sensitisation and work-related respiratory symptoms[44]. However, the role atopy plays as a risk for developing occupational asthma to low molecular weight agents remains much less well understood. Whilst atopy is recognised as a risk factor, it is a common finding in working populations (approximately 30% of working people have atopy) and is not generally considered in deciding whether or not someone is fit for work.

Several genetic influences have been identified. For example, various genetic influences (primarily associated with the human leukocyte antigen gene complex) are described for isocyanate-related asthma,

Figure 1: definitions of work related asthma types



** The following fuller definition of work-aggravated asthma is often cited and used: 'Worsening of asthma due to conditions at work, regardless of frequency or duration of worsened asthma, and regardless whether there are permanent changes in asthma severity.'*[28]

*** For a full description please see the review by Vandenplas et al*[18].

but also for conditions caused by exposure to anhydride acids[45], platinum salts[46] and western red cedar[47]. Again, to our knowledge, no workplaces currently exclude workers on the basis of genetic testing, but the evidence base is extremely helpful to develop an understanding of how occupational asthma develops.

The presence of rhinitis, asthma or airway hyper reactivity (irritable lungs associated with asthma) also appear to be risk factors for going on and developing occupational asthma. The development of rhinitis, particularly in high molecular weight agent exposed workers, appears to be particularly important as risk factor for subsequent development of asthma[48,49,50,51]. It is not appropriate, for example, to exclude a possible diagnosis of occupational asthma just because the worker had asthma prior to the relevant exposure period.

CONCLUSION

Occupational asthma remains a relatively common work-related lung disease and workplace exposures are thought to be responsible for 15% of the burden of adult-onset asthma. This equates to approximately one in every six cases of asthma. There are many identified causes, but the top five in the UK remain: isocyanates; flour; cleaning agents; wood dusts; and enzymes/amylase. The majority of cases in reporting schemes are associated with typical or common causes, but novel and new causes are continually described.

Other than exposure to an agent capable of causing asthma itself, the only clinically important risk factor is atopy, which appears to increase the risk of developing occupational asthma when exposed to high molecular weight agents. Workers who develop rhinitis because of workplace exposures are also at an increased risk of developing occupational asthma. While various genetic risk factors also appear important for specific causes, to our knowledge workers are not being excluded on the basis of such testing, and it remains our view that this would not be appropriate.

To identify this condition early[52], and ultimately to prevent further cases, clinicians must be vigilant in relation to work as a cause of asthma, and proactively investigate this potential link where appropriate. The

diagnosis of occupational asthma will be dealt with in the next article in the series. ■

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The contents of this article reflect the views of the authors alone and not necessarily those of HSE policy.

Further information

- HSE online information on asthma: www.hse.gov.uk/asthma
- OASYS and occupational asthma: www.occupationalasthma.com
- Canadian Centre for Occupational Health and Safety – includes a detailed list of potentially causative agents: ohaw.co/CCOHSasthma
- Health and Safety Laboratory Group of Occupational Respiratory Disease Specialists (GORDS): ohaw.co/GORDS

CONCLUSIONS

- **A significant** proportion of adult-onset asthma is caused by inhaled exposures at work, with 15% of all asthma attributed to work, or on average one in six
- **The term** occupational asthma includes asthma caused by work due to (i) sensitisation and (ii) very high dose irritant exposures; the latter is called acute irritant induced asthma
- **Asthma** not caused by work can also be aggravated by exposures at work. The nature of these aggravating exposures is broad, and not confined to inhaled exposures. For example, work-related stress and changes in workplace temperature are also described as influencing asthma at work
- **There are** many causes of occupational asthma, but most reported cases are due to isocyanates (activated paints), flour, cleaning agents, wood dusts and enzymes
- **Other than** exposure to an inhaled substance capable of causing the condition, atopy, asthma, airway reactivity and rhinitis have all been identified as risk factors for occupational asthma, with varying degrees of evidence. Gender and smoking do not appear to be important risk factors
- **While** certain specific causes of occupational asthma have been associated with a genetic influence (for example asthma caused by exposure to acid anhydrides), the generally accepted view is that workplaces should be safe for all workers, and that genetic testing is not appropriate to assess risks
- **Occupational** asthma is almost entirely preventable. Key to this aspiration are factors that influence reduction in exposures to agents that are able to cause asthma, developing good-quality methods for identifying and managing early cases, and feeding back health-outcome information into workplace-based risk assessment processes

Notes

1 Francis HC, Prys-Picard CO, Fishwick D et al. Defining and investigating occupational asthma: a consensus approach. Occupational and Environmental Medicine 2007; 64: 361–365.

2 Fishwick D, Barber CM et al. Standards of care for occupational asthma: an update. Thorax 2012; 67: 278–280. ohaw.co/Fishwick2012.

3 British Thoracic Society/SIGN. British guideline on the management of asthma: a national clinical guideline. SIGN 141. Edinburgh: Health Improvement Scotland/Intercollegiate Guidelines Network, 2014. ohaw.co/BTSasthma.

4 Jacobs J, Meijster T et al. Wheat allergen exposure and the prevalence of work-related sensitisation and allergy. Allergy 2008: 63: 1597–1604.

5 Brisman J, Järvholm B, Lillienberg L. Exposure-response relations for self reported asthma and rhinitis in bakers. Occupational and Environmental Medicine 2000; 57: 335–340.

6 Heederik D, Houba R. An exploratory quantitative risk assessment for high molecular weight sensitizers: wheat flour. Annals of Occupational Hygiene 2001; 45(3): 175–185.

7 Henneberger PK, Cumro D et al. Beryllium sensitization and disease among long-term and short-term workers in a beryllium ceramics plant. International Archives of Occupational and Environmental Health 2001; 74(3): 167–76.

8 Nicholson PJ, Cullinan P et al. Evidence based guidelines for the prevention, identification, and management of occupational asthma. Occupational and Environmental Medicine 2005; 62: 290–299.

9 Nicholson PCP, Burge P, Boyle C. Occupational asthma: prevention, identification and management. Systematic review and recommendations. London: British Occupational Health Research Foundation, 2010. ohaw.co/BOHRFasthma (accessed 9.2.2018).

10 Bradshaw LM, Barber CM et al. Work-related asthma symptoms and attitudes to the workplace. Occupational Medicine 2007; 57(1): 30–35.

11 Cannon J, Cullinan P, Newman Taylor A. Consequences of occupational asthma. BMJ 1995; 311: 602–603.

12 Boyd R, Cowie H et al. The true cost of occupational asthma in Great Britain. Health and Safety Executive Research Report 474. Sudbury: HSE Books 2006. ohaw.co/HSEcostOccAst (accessed 25.1.2018).

13 Walters GI, McGrath EE, Ayres JG. Audit of the recording of occupational asthma in primary care. Occupational Medicine 2012; 62: 570–573.

14 Fishwick D, Bradshaw L et al. Are we failing workers with symptoms suggestive of occupational asthma? Primary Care Respiratory Journal 2007; 16: 304–310.

15 Cone JE, Wugofski L et al. Persistent respiratory health effects after a metam sodium pesticide spill. Chest 1994; 106(2): 500–508.

16 Kern DG. Outbreak of the reactive airways dysfunction syndrome after a spill of glacial acetic acid. American Review of Respiratory Disease 1991; 144: 1058–1064.

17 Wheeler K, McKelvey W et al. Asthma diagnosed after 11 September 2001 among rescue and recovery workers: findings from the World Trade Center Health Registry. Environmental Health Perspectives 2007; 115(11): 1584–1590.

18 Vandenplas O, Wiszniewska M et al. EAACI position paper: irritant-induced asthma. Allergy 2014; 69: 1141–1153.

19 Fishwick D. Work aggravated asthma; a review of the recent evidence. British medical Bulletin 2014; 110(1): 77–88.

20 Bradshaw L, Sumner J et al. Work aggravated asthma in Great Britain; a cross sectional postal survey. Primary Health Care Research & Development 2018; online first: doi: 10.1017/S1463423618000063.

21 Fishwick D, Barber CM, et al. Standards of care for occupational asthma: an update. Thorax 2012; 67: 278–280.

22 Balmes J, Becklake M et al. Environmental and Occupational Health Assembly, American Thoracic Society. American Thoracic Society Statement: occupational contribution to the burden of airway disease. American Journal of Respiratory and Critical Care Medicine 2003; 167(5): 787–97. ohaw.co/ATS2003

23 Feary J, Pinnock H, Cullinan P. Occupational asthma. BMJ 2016; 353: i2658.

24 Kogevinas M, Zock J et al. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). Lancet 2007; 370: 336–341.

25 Mackie J. Effective health surveillance for occupational asthma in motor vehicle repair. Occupational Medicine 2008; 58: 551–555.

26 Collins JJ. Incidence of occupational asthma and exposure to toluene diisocyanate in the United States toluene diisocyanate production industry. Journal of Occupational and Environmental Medicine 2017; 59(Suppl 12): S22–S27.

27 Henneberger PK, Olin AC et al. The incidence of respiratory symptoms and diseases among pulp mill workers with peak exposures to ozone and other irritant gases. Chest 2005; 4: 3028–3037.

28 Henneberger PK, Redlich CA et al; ATS Ad Hoc Committee on Work-Exacerbated Asthma. An official American Thoracic Society Statement: work-exacerbated asthma. American Journal of Respiratory and Critical Care Medicine 2011; 184(3): 368–378. ohaw.co/ATS2011

29 Health and Safety Executive. Work related asthma in the UK. Updated November 2017. www.hse.gov.uk/statistics/causdis/asthma/ (accessed 25.1.2018).

30 Surveillance of Work Related and Occupational Respiratory Diseases (SWORD) scheme. University of Manchester, UK. ohaw.co/SWORD (accessed 25.1.2018).

31 Fishwick D, Barber CM, Bradshaw LM, et al. Standards of care for occupational asthma: an update. Thorax 2012; 67: 278–280.

32 Ghosh RE, Cullinan P, Fishwick D, Hoyle J, Warburton CJ, Strachan DP, Butland BK, Jarvis D. Asthma and occupation in the 1958 birth cohort. Thorax 2013; 68(4): 365–371.

33 Fishwick D. New occupational and environmental causes of asthma and extrinsic allergic alveolitis. Clinics in Chest Medicine 2012; 33(4): 605–616.

34 Cummings KJ, Gaughan DM et al. Adverse respiratory outcomes associated with occupational exposures at a soy processing plant. European Respiratory Journal 2010; 36(5): 1007–1015.

35 Harris-Roberts J, Robinson E et al. Sensitization and symptoms associated with soybean exposure in processing plants in South Africa. American Journal of Industrial Medicine 2012; 55(5): 458–464.

36 Sabrià J, Antó JM et al. Clinical and functional characteristics of patients two years after being affected by the soybean asthma epidemic in Barcelona. Thorax 1994; 49(9): 906–909.

37 Cullinan P, Harris JM et al. An outbreak of asthma in a modern detergent factory. Lancet 2000; 356: 1899–1900.

38 Heffler E, Nebiolo F et al. Occupational asthma caused by Neurospora sitophila sensitization in a coffee dispenser service operator. Annals of Allergy, Asthma & Immunology 2009; 102(2): 168–169.

39 Bernedo N, García M et al. Allergy to laxative compound (Plantago ovata seed) among health care professionals. Journal of Investigational Allergology and Clinical Immunology 2008; 18(3): 181–189.

40 Granslo JT, Van Do T et al. Occupational allergy to Artemia fish fry feed in aquaculture. Occupational Medicine 2009; 59(4): 243–248.

41 Viinanen A, Salokannel M, Lammintausta K. Gum arabic as a cause of occupational allergy. Journal of Allergy (Cairo) 2011; 2011: 841508.

42 Glass WI, Power P et al. Work-related respiratory symptoms and lung function in New Zealand mussel openers. American Journal of Industrial Medicine 1998; 34(2): 163–168.

43 Vandenplas O. Occupational asthma: etiologies and risk factors. Allergy, Asthma & Immunology Research 2011; 3(3): 157–167.

44 Jacobs J, Meijster T et al. Wheat allergen exposure and the prevalence of work-related sensitisation and allergy. Allergy 2008: 63: 1597–1604.

45 Young RP, Barker RD et al. The association of HLA-DR3 with specific IgE to inhaled acid anhydrides. American Journal of Respiratory and Critical Care Medicine 1995; 151: 219–221.

46 Newman Taylor AJ, Cullinan P et al. Interaction of HLA phenotype and exposure intensity in sensitization to complex platinum salts. American Journal of Respiratory and Critical Care Medicine 1999; 160: 435–438.

47 Horne C, Quintana PJ et al. Distribution of DRB1 and DQB1 HLA class II alleles in occupational asthma due to western red cedar. European Respiratory Journal 2000; 15: 911–914.

48 Descatha A, Leproust H et al. Factors associated with severity of occupational asthma with a latency period at diagnosis. Allergy 2007; 62: 795–801.

49 Gautrin D, Infante-Rivard C et al. Incidence and host determinants of probable occupational asthma in apprentices exposed to laboratory animals. American Journal of Respiratory and Critical Care Medicine 2001; 163: 899–904.

50 Gautrin D, Ghezzo H et al. Long-term outcomes in a prospective cohort of apprentices exposed to high-molecular-weight agents. American Journal of Respiratory and Critical Care Medicine 2008; 177: 871–879.

51 Vandenplas O, Van Brussel P et al. Rhinitis in subjects with work-exacerbated asthma. Respiratory Medicine 2010; 104: 497–503.

52 Fishwick D, Forman S. Health surveillance for occupational asthma (review article). Current Opinion in Allergy and Clinical Immunology 2018; 18(2): 80–86.