BAKER'S ALLERGY AND ASTHMA – A REVIEW OF THE LITERATURE

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ABSTRACT
Asthma caused by allergy to proteins from cereal grains is one of the most common types of occupational asthma (OA) worldwide and its prevalence does not appear to be declining. Baker's asthma is the most serious manifestation of occupational allergy among bakery workers, which develops after inhalational exposure to flour dust allergens encountered in the work environment. Exposure to cereal flours such as wheat and rye, as well as enzymes, has been reported to play an important role. However, more recently several other salt-soluble, insoluble proteins and recombinant allergens have been implicated. Exposure response studies have demonstrated consistent evidence that the risk of developing occupational allergy increases with allergen exposure, and this relationship is modified by atopic status. Despite the overwhelming evidence that workplace exposures to flour dust should be controlled, prevention strategies in bakeries appear not to have been very satisfactory. The review describes current regulatory standards and preventative strategies, noting that the South African exposure standards are not protective and do not follow international best practice. While total avoidance of flour dust exposure is not possible in bakeries, exposure reduction is the preferred pragmatic approach. Various exposure reduction strategies that have been recently reported in the literature are reviewed with a view to optimising preventive approaches.

INTRODUCTION

Asthma caused by cereal grains, such as baker's asthma, is one of the most common forms of occupational asthma (OA), and its prevalence does not appear to be declining.[1] In 1700 Ramazzini wrote the first scientific report on baker's asthma.[2] It was only in the 20th century (1909) that allergic sensitisation by skin reactivity to wheat extracts was demonstrated in a baker with asthma. In 1929 de Besche introduced baker's asthma as an allergic disease for the first time.[3] Baker's asthma is not only confined to bakers, since exposure to these allergens can result in the development of the disease and can be present in confectioners, pastry factory workers, flour millers and food processors.[4] Exposure to cereal flours such as wheat and rye, but also enzymes, have been reported to play an important role. Subsequent studies have identified several wheat flour proteins as allergens in sensitised bakers with asthma.[5,6]

THE BAKING PROCESS AND HIGH-RISK ENVIRONMENTAL EXPOSURE SETTINGS

Occupational exposure to flour occurs mainly in bakeries, flour mills, food-producing and processing industries, and related industries such as enzyme-producing and baking-ingredient industries. Many bakeries are located in supermarkets or are traditional small-scale craft bakeries. Besides bread, products such as cakes, biscuits and pastry are produced. Flour, and also yeast, spices and additives are used as main ingredients. The production process includes activities such as sifting of flour, making dough, cutting and shaping, baking, cooling and storing. Ingredients that are potentially allergenic are wheat flour, rye flour, fungal α-amylase, enzymes, soya flour, malt flour, gluten and sesame seeds.

Results of exposure studies demonstrate that workers at the front end of the baking process, such as bakers and dough makers, generally have the highest (8-hour average) dust exposures.[7,8] Activities like sieving, weighing and mixing are associated with high dust exposures.[9] Cleaning operations, and bread and roll production also result in high exposures.[10] Peak exposures are caused by dusting during dough forming (to prevent dough adhesion to surfaces) or by adding ingredients into the dough mixer (Fig. 1). The relationship between dust and wheat antigen exposure varies considerably, depending on the specific bakery occupation, the size of the bakery, and the type of product produced by the bakery.[11]

CONSTITUENTS OF FLOUR DUST – POTENTIAL ALLERGENS AND THEIR SOURCES

Flour and its additives contain many potential allergens, which include components of wheat flour as well as flour

Fig. 1. Examples of activities that cause high (top) and low (bottom) flour-dust exposures in bakeries.

contaminants such as mites, weevils and moulds.[12] Well-known high-molecular-weight sensitisers are wheat proteins and baking additives such as enzymes (e.g. *Aspergillus*-derived) fungal α-amylase.[13] A recent review by Quirce *et al.* (2013), reported that proteins represent 10-15% of wheat grain, and that the salt-soluble fractions, viz. albumins and globulins, comprise only 15-20% of the total protein.[1] With increasing modernisation and innovations in the baking industry over the last few decades, and the introduction of new ingredients, the list of causative agents in baker's asthma has also expanded. Table I lists potential allergen sources, including non-flour-related products, associated with exposure among bakery workers.

EPIDEMIOLOGY OF ALLERGIC SENSITISATION AND ASTHMA ASSOCIATED WITH FLOUR DUST

It is well documented that exposure to flour dust increases the risk of allergic sensitisation and lung diseases, particularly OA.

ALLERGIC SENSITISATION

CEREALS

Wheat flour protein allergens are reported to be responsible for 60-70% of all cases of workers reporting work-related respiratory symptoms.[5] The review by Houba *et al.*[14] reported prevalence of sensitisation to wheat flour ranging from 5% to 28%, in epidemiological studies from 1967 to 1998. More recent studies show the incidence of sensitisation to flour is estimated to be between 2.2% and 4.2% per person year (pyr).[1,15] However, most of these studies were conducted in large industrial bakeries or milling plants. With specific reference to supermarket bakeries, a British study reported the IgE reactivity to flour (11%) of bakery employees, which was similar to small Italian and craft bakeries (12-24%).[8,16,17] The majority of bakers with workplace-related asthma or rhinitis are sensitised to wheat or rye flour. One such study of baker's asthma reported that bakers with workplace-related respiratory symptoms showed mainly sensitisation to wheat flour (64%), rye flour (52%) and soybean flour (25%).[18] It has

Table I. Potential allergen sources associated with baker's allergy and asthma

Cereal flours
Wheat
Rye
Barley
Cereal malt flour
Rice flour
Non-cereal flours
Soybean flour
Buckwheat
Lecithin (from soybean)
Baking additive enzymes
α-amylase
Glucoamylase
(Hemi) cellulase
Protease
Xylanase
Papain
Glucose oxidase
Moulds and yeast
Aspergillus, Alternaria
Baker's yeast
Other additives
Egg material yolk
Egg white
Almond, hazelnuts
Cocoa
Milk powder
Sesame seeds
Chocolate
Insects
Storage mites
Grain weevil
Flour beetle
Cockroach
Flour moth

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also been shown that sensitisation precedes the onset of upper and lower airway symptoms, and asthma.[19]

ENZYMES

Exposure to fungal α-amylase has been reported as an important risk factor in British bakeries and flourmills for the development of OA.[20] Fungal α-amylase is routinely added to flour to speed up the baking process and improve bread quality. Several case reports have been reported of baker's asthma caused by this enzyme, often in the absence of specific IgE to cereal allergens.[21-23] The prevalence of sensitisation varies from 2% to 16% for fungal α-amylase.[7] An epidemiological study in British supermarket bakeries found that 5% of the workers had positive skin-prick test to α-amylase whereas an Italian craft bakery study reported a slightly higher prevalence of 7.5%.[8,24] Vanhanen *et al.*[25] in their study on enzyme exposure and enzyme sensitisation in the bakery industry found that 8% of workers in bakeries, 5% in flourmills, and 3% in crispbread production were sensitised to enzymes such as cellulose and xylanase. The incidence of sensitisation to fungal α-amylase is estimated to be 25 cases per 1 000 pyrs (2.5%).[15] Baur *et al.* in their studies relating to α-amylase exposure found that 24-55% of bakers with respiratory symptoms who were attending medical services, were sensitised to α-amylase.[26-28]

STORAGE MITES

Wheat flour in bakeries can be contaminated with storage mites, which have been suggested as another cause of allergic symptoms in bakery workers.[29] A number of epidemiological studies show a high prevalence of sensitisation to storage mites (*Acarus siro, Glycyphagus domesticus, Lepidoglyphys destructor, Tyrophagus longior,* and *Tyrophagus putrescentiae)* in bakery workers, varying between 11% and 33%;[16,24,25] however Tee[30] suggested that cross-reactivity with house-dust mite may be the main reason for immunological reactivity observed in bakery workers.

SPECIFIC ALLERGENS IDENTIFIED

With increasing technology available over the years in the investigation of baker's asthma, purified wheat proteins either in natural or recombinant forms have been implicated in the pathogenesis of baker's asthma. Sander *et al.*[5] identified more than 100 IgE-binding protein spots associated with baker's asthma, and demonstrated reactions in sera from sensitised bakers to many of these antigens. Weichel *et al.*[31] demonstrated that wheat thioredoxin hb (Tri a 25) is a novel cross-reactive allergen that may contribute to the symptoms of baker's asthma, while Palacin *et al.*[32] reported recombinant wheat lipid transfer protein (Tri a 14) as an important allergen and a potential tool for baker's asthma diagnosis. Lehto *et al.*[33] demonstrated reactions to α-amylase inhibitor, peroxidase, thaumatin-like protein, and to lipid transfer protein 2G. More recent reviews by Salcedo *et al.*[34] and Quirce *et al.*[1] summarised these studies which have identified several other salt-soluble proteins (albumins and globulins) such as cereal α-amylase/trypsin inhibitors, peroxidase, thioredoxin, nonspecific lipid transfer protein, serine proteinase inhibitor, and thaumatin-like protein; salt-insoluble storage proteins (prolamins, namely, gliadins and glutenins); and recombinant allergens as the allergens associated with baker's asthma.

RESPIRATORY SYMPTOMS AND ASTHMA

RHINITIS

Studies among Swedish trainee bakers estimated incidence rates of 29.4 cases per 1 000 pyrs for rhinitis,[35,36] while a British study reported incidence rates of work-related ocular-nasal symptoms of 118/1 000 pyrs.[15] Various epidemiological studies have consistently reported that rhinitis is a significant risk factor for adult-onset asthma, for both work-related and non-work-related disease outcomes and that the appearance of ocular-nasal symptoms could be used to identify workers at increased risk of developing OA.[37-39] Previous studies have shown that 11.5% of subjects with occupational rhinitis develop OA, and specifically 11.6% of these individuals are exposed to flours and grains.[37] Comorbid rhinitis or rhino-conjunctivitis has been reported in a greater proportion (45-90%) of subjects suffering from IgE-associated OA and has been attributed to various sensitisers including flour dust.[40]

ASTHMA

Various phenotypes of work-related asthma have been described, including OA and work-aggravated asthma.[41] Studies conducted among bakery workers have documented a prevalence of respiratory symptoms varying between 5% and 21%.[12,16,24,25] The reported prevalence of bronchial hyper-responsiveness ranges between 25% and 40%.[42-44]

The positive association of sensitisation to bakery allergens and work-related symptoms in baker's asthma has been further demonstrated in a nested case-control study of bakery students,[45] as well as in an industrial and small bakery setting using a referent population from the petrochemical industry.[46] Quirce *et al.*[47] demonstrated that a positive skin-prick test to an occupational allergen and nonspecific bronchial hyper-responsiveness (NSBH) correlated with a positive specific inhalation test to flour dust. Specific inhalation challenge tests performed in 160 bakers with suspected baker's asthma, demonstrated positive test for early asthma in 42 subjects (26%) and for late/dual asthma in 18 (11%).[48] Baatjies *et al.* recently demonstrated that sensitisation to wheat was the strongest predictor of allergic airway inflammation, as measured by exhaled nitric oxide measurements in bakery workers, confirming that the allergic asthma phenotype is the predominant phenotype in baker's asthma.[41,49]

The prevalence of probable OA in epidemiological studies ranges between 4% and 13% in various studies of industrial bakeries in which a similar definition of OA (bronchial hyper-responsiveness and sensitivity to flour) was used.[8,50] Incident studies of baker's asthma have reported rates of 3-41 cases per 1 000 pyrs.[15,36] A recent study of the incidence of baker's asthma among young bakers reported a range from 0.3 to 2.4 cases per 1 000 pyrs.[51]

EXPOSURE LEVELS OF DUST AND FLOUR ALLERGENS IN BAKERIES

DUST LEVELS

The inhalable flour dust concentrations for the different occupational titles across studies are outlined in Table II. The results demonstrate that workers at the front end of the baking process (dough makers, bread formers) have the highest 8-hour average dust exposures (average inhalable dust exposures of 2-9 mg/m^3). For oven workers the exposure levels ranged from 0.6 to 3.2 mg/m^3. Bakery workers with tasks that involved slicing and packaging of bread or other products had exposure levels around 1 mg/m^3.

Nieuwenhuijsen *et al.*[52] conducted a study in bakeries and flour mills and demonstrated that the areas with the highest exposure levels were confectionery (dough brake), dispensing/mixing, and bread production with exposure levels of 6.1 mg/m^3, 3.8 mg/m^3, and 1.4 mg/m^3 respectively. A study conducted by Burdorf *et al.*,[53] employing a task-based grouping strategy, found a clear hierarchy in geometric mean exposure levels among bakery workers, in descending order of exposure: dough makers (5.5 mg/m^3), bread formers (2.7 mg/m^3), oven workers (1.2 mg/m^3), packers and confectionery workers (0.5 mg/m^3) (Table II).

WHEAT ALLERGEN

Studies of exposure to wheat flour allergens are summarised in Table III. The highest exposure levels were found among dough makers and workers involved in bread production. Bulat *et al.*[54] found the highest exposure levels among traditional bakeries in bread production (22.33 µg/m^3) as well as bread and pastry production (14.48 µg/m^3).

RYE

Only one study reported a detailed exposure characterisation of rye allergen exposures among bakery workers (Table III). In this study, bakers had the highest average geometric mean (GM) exposure (5.14 µg/m^3), followed by confectioners (2.98 µg/m^3), supervisors (2.16 µg/m^3) and managers (2.52 µg/m^3), with counterhands having the lowest exposures (0.98 µg/m^3).[55] This study also demonstrated a very strong correlation between wheat and rye allergen concentrations (Pearson r=0.98, $p<0.001$).

Table II. Exposure characterisation of dust particulate measurements in bakeries according to occupational titles								
Study author (year)	**Sampling time (hours)**	**Sampling head (dust fraction)**	***N***	***n***	**Occupational title**	**GM or AM**	**GSD or SD**	**Range (µg/m³)**
Hartmann (1986)	3	NR	31	31	All	NR	NR	0.2 -19.8
Masalin *et al.* (1988)	NR	NR	29	29	All	NR	NR	0.1-8.8
Musk *et al.* (1989)	Full-shift	Casella or Millipore (total dust)	79	10 16	Doughmakers Oven staff	2.7 1.7	NR NR	0.6-14.1 0.0-37.6
Jeffery (1992)	Full-shift	7-hole or Casella (inhalable/total dust)	68	3 16	Weighing/mixing Dividing/moulding	8.6 4.7	2.3 2.0	3.3-15.8 1.6-19.1
Jauhiainen *et al.* (1993)	4-7	3-piece cassettes (total dust)	20	13	Making of dough Making of bread	4.6* 2.3*	3.6* 0.9*	0.9-14.7 1.5-3.4
Kolopp-Sarda *et al.* (1994)	NR	NR	10	10	All	4.9*	9.1*	NR
Bohadana *et al.* (1994)	4	Millipore (total dust)	21	14 6	General baker Oven handler	3.4* 1.1*	3.7* 0.9*	0.7-8.7 0.5-2.7
Lillienberg and Brisman (1994)	Full-shift	IOM (inhalable)	29	6 3 10	Dough mixing Oven control Dough forming	7.5* 3.2* 2.5*	5.4* 1.7* 0.8*	NR NR NR
Burdorf *et al.* (1994)	1-7	IOM (inhalable)	129	34 62 10	Dough makers Bread formers Oven workers	5.5† 2.7† 1.2†	2.1† 2.0† 2.4†	1.2-16.9 0.6-14.2 0.2-4.0
Nieuwenhuijsen *et al.* (1994)	Full-shift	7-hole (inhalable)	352	24 32	Dispense/mixing Roll production	5.0 2.4	2.5 2.5	1.4-86.0 0.4-21.1
Houba *et al.* (1996)	Full-shift	PAS-6 (inhalable)	546	105 66 27 81 20 132	Dough makers All-round staff Maintenance Oven staff Production managers Slicers, packers	3.0 0.9 0.7 0.6 0.6 0.4	2.3 NR NR 2.2 NR NR	0.4-37.7 0.1-26.8 0.3-5.5 0.1-5.1 0.1-4.9 0.1-2.8
Vanhanen *et al.* (1996)	Full-shift‡	Milipore (total dust)	30	7 10	Dough making Bread making	8.4* 3.2*	NR NR	3.0-18.8 1.2-5.5
Burstyn *et al.* (1997)	Full-shift	7-hole (inhalable)	96	96	All bakers using flour	2.1	5.1	0.1-110
Elms *et al.* I (2003)	Full-shift	IOM (inhalable)	117	13 3 29 21 5 8 9	Weigher Pastries Mixer Baker Confectionery Ovens Packer	11.4§ 11.2§ 7.6§ 6.3§ 4§ 2.1§ 0.8§	NR NR NR NR NR NR NR	2.4-26.3 2.5-13.3 1.0-36.8 <LOD-27.8 0.6-8.2 <LOD-18.0 <LOD-2.2
Bulat *et al.* (2004)	Full-shift	PAS-6 (inhalable)	300	29 57 22 31	Bread production Pastry production Baker Packaging	2.10 1.11 1.06 0.56	2.42 2.55 3.61 2.09	0.30-13.30 0.23-8.70 0.17-8.52 0.22-2.17
Elms *et al.* (2005)	Full-shift	IOM (inhalable)	208	108 59 6 35	Baker/dough brake Mixer/siever Cleaner Other	3.3 4.7 3.8 2.2	3.4 3.4 3.5 2.8	<LOD-47.0 <LOD-30.6 0.4-14.3 <LOD-30.8
Elms *et al.* (2006)	Full-shift	IOM (inhalable)	195	100 55 6 34	Baker/table Mixer/siever Cleaner Other	3.3 4.7 3.8 2.2	NR NR NR NR	NR NR NR NR
Meijster *et al.* (2008)	Full-shift	PAS-6 (inhalable)		30 4 16 8 1	Bread baker Pastry maker Dough maker All baker Storage worker	4.49 0.49 1.82 2.02 2.32	NR NR NR NR NR	NR NR NR NR NR
Baatjies *et al.* (2010)	Full-shift	PAS-6 (inhalable)	211	112 38 13 13 35	Bread baker Confectioner Supervisor Manager Counterhand	1.33 0.65 0.56 0.51 0.28	2.25 2.08 2.05 2.34 1.89	0.25-7.29 0.11-3.33 0.20-2.67 0.12-2.48 0.11-1.96

N = total numb er of personal samples; *n* = number of samples taken in occupational title; AM = arithmetic mean; GM = geometric mean; SD = standard deviation; GSD = geometric standard deviation;* = concentration and standard deviation in AM and SD (all others GM and GSD); † = GM and GSD could be biased because of large variations in sampling time; ‡ = sampling time varied from 2 to 4 hours but several consecutive personal samples were taken to cover the whole working shift; § = median level of exposure, NR = not reported.

Table III. Exposure characterisation of allergen measurements in bakeries according to occupational titles

Allergen type Study author (year)	Sampling time (hours)	Sampling head (dust fraction)	*N*	*n*	Occupational title	GM	GSD	Range
Wheat flour (µg/m^3)								
Nieuwenhuijsen *et al.* (1994)	Full-shift	Casella (inhalable)	495	24	Dispensing/mixing	228.7	2.4	25.9-842.97
				32	Roll production	215.3	1.8	71.1-1015.3
				9	Dough brake	208.5	3.0	36.1-1912.7
				45	Bread production	176.6	2.3	43.9-744.3
				36	Hygiene inside	148.6	3.8	15.4-4506.3
Houba *et al.* (1996)*	Full-shift	PAS-6 (inhalable)	449	76	Dough makers	5232	NR	33–252,407
				54	All-round staff	992	NR	33-68 159
				17	Production managers	505	NR	33-74 614
				71	Oven staff	322	NR	33-28 079
				20	Maintenance	242	NR	33-2 539
				109	Slicers, packers	77	NR	33-7 736
Bulat *et al.* (2004)	Full-shift	PAS-6 (inhalable)	300					
				20	Baker	6.15	3.57	1.5-100.3
				32	Packaging	2.79	2.25	0.5-48.44
				30	Bread production	22.33	2.97	1.9-171.23
				138	Bread and pastry	14.48	3.75	0.46-205.9
				60	Pastry production	8.71	4.16	0.58-150.7
Baatjies *et al.* (2010)	Full-shift	PAS-6 (inhalable)	211	112	Bread baker	13.66	2.66	1.79-69.65
				38	Confectioner	5.82	2.25	0.82-30.68
				13	Supervisor	4.99	1.93	2.28-17.79
				13	Manager	3.41	4.01	0.32-40.28
				35	Counterhand	1.16	4.81	0.002-29.86
Rye flour (µg/m^3)								
Baatjies *et al.* (2010)	Full-shift	PAS-6 (inhalable)	211	112	Bread baker	5.14	2.89	0.30-31.08
				38	Confectioner	2.04	2.41	0.24-12.96
				13	Supervisor	1.74	1.97	0.61-6.84
				13	Manager	1.99	4.06	0.09-9.32
				35	Counterhand	0.39	4.57	<LOD-10.9
Houba *et al.* (1997)	Full-shift	PAS-6 (inhalable)	507	32	Dough makers	0.8	5.14	<LOD-33.1
				35	All-round staff	0.2	2.35	<LOD-14.3
				77	Oven staff	0.2	1.45	<LOD-2.3
				119	Slicers, packers	0.2	1.44	<LOD-8.8
				27	Maintenance	0.2	1.33	<LOD-0.7
				20	Production managers	All < LOD		
Nieuwenhuijsen *et al.* (1999)	Full-shift	Casella (inhalable)	478	3	Dispensing/mixing	39.7	2.2	NR
				14	Hygiene (inside)	1.5	4.3	NR
				11	Roll production	1.0	5.3	NR
				23	Bread production	0.4	5.4	NR
				21	Bread wrapping	0.1	1.3	NR
Fungal alpha-amylase (ng/m^3)								
Elms *et al.* (2003)	Full-shift	IOM (inhalable)	117	13	Weigher	29.1[†]	NR	<LOD-1370
				29	Mixer	3.2[†]	NR	<LOD-123
				21	Baker	1.6[†]	NR	<LOD-185
				8	Ovens	1.5[†]	NR	<LOD-3.2
				9	Packer	1.4[†]	NR	<LOD-2.1
				3	Pastries	1.1[†]	NR	<LOD-1.5
				5	Confectionery	All < LOD		
Bulat *et al.* (2004)	Full-shift	PAS-6 (inhalable)	300	29	Bread production	0.61	3.89	0.11-17.65
				20	Baker	0.47	7.19	0.11-36.16
				59	Pastry production	0.47	4.04	0.10-51.13
				32	Packaging	0.15	1.74	0.11-1.24
Elms *et al.* (2006)	Full-shift	IOM (inhalable)	195	100	Baker/table	1.7	NR	NR
				55	Mixer/siever	NR	NR	NR
				6	Cleaner	NR	NR	NR
				34	Other	NR	NR	NR
Baatjies *et al.* (2010)	Full-shift	PAS-6 (inhalable)	211	112	Bread baker	0.15	2.32	LOD-19.62
				38	Confectioner	0.12	2.14	LOD-6.54
				13	Supervisor	0.10	1.17	LOD-1.17
				13	Manager	0.12	1.58	LOD-0.51
				35	Counterhand	0.11	1.40	LOD-0.64

N = total number of personal samples; *n* = number of samples taken in occupational title; GM = geometric mean; GSD = geometric standard deviation; LOD = limit of detection; ∗ = wheat allergen concentration in ng/m^3; † = median level of exposure, NR = not reported.

FUNGAL α-AMYLASE

A British study reported considerable differences between levels of exposure to fungal α-amylase between exposure groups, with workers employed in dispensing and mixing areas having the highest exposure (39.7 ng/m^3) (Table III). Houba *et al.*[56] found the highest fungal α-amylase exposures among dough makers producing crispbakes GM 18.1 ng/m^3), followed by dough makers in wheat bread production (GM 0.8 ng/m^3), as well as bread and mixed bakers in small bakeries (0.2-0.3 ng/m^3). Another British study found that mixers and weighers had significantly higher levels of fungal α-amylase (3.2-29.1 ng/m^3), compared with other job categories (p<0.01).[57] This trend was also identified by Nieuwenhuijsen *et al.*[20] and Vanhanen *et al.*[58] who reported the highest levels of fungal α-amylase exposure in dough-making areas of the bakery. Similarly, it has been demonstrated that bread production workers had the highest exposure (0.61 ng/m^3), compared with packaging workers (0.15 ng/m^3).[54]

ENVIRONMENTAL RISK FACTORS AND EXPOSURE-RESPONSE RELATIONSHIPS FOR FLOUR DUST AND BAKER'S ASTHMA

There is consistent evidence that the risk of developing occupational allergy increases with allergen exposure.[59] However, this exposure-response relationship is complex. In earlier studies the frequency of sensitisation to wheat flour and α-amylase increased with intensity of dust exposure as well as wheat allergen exposure.[24] A strong, positive association has been demonstrated between wheat flour allergen exposure and wheat-flour-specific allergic sensitisation.[11] Similarly a strong and positive association has been found between fungal α-amylase allergen exposure levels and specific allergic sensitisation.[60]

These studies provided the first evidence supporting a dose-response relationship between the exposure level to wheat and fungal α-amylase and the development of sensitisation and work-related respiratory symptoms. The demonstration of dose-response relationships is of importance in determining permissible concentrations for prevention.[61] However, there are uncertainties in respect of the relative importance of peak vs average levels of exposure, the risk of sensitisation at low concentrations (i.e. the 'no-effect level'), and the shape of the dose-response curve.

Studies investigating the shape of the relationship between flour dust exposure and wheat allergen levels suggest that the dose-response relationship for sensitisation may be non-linear and may even level off or decline at higher exposure levels.[62, 63, 64] There have been no clear indications of an exposure level below which the risk for sensitisation is zero or negligible.

HOST-ASSOCIATED RISK FACTORS FOR ALLERGIC SENSITISATION AND ASTHMA ASSOCIATED WITH FLOUR DUST

Various studies have reported that only a small proportion of workers develop OA, although these workers have similar workplace exposures. This suggests that potential underlying differences in individual susceptibility due to host-specific factors are also important considerations. The host factors that have been incriminated in the development of OA are outlined below.

GENETICS

Several genetic studies have demonstrated an association between certain human leucocyte antigen (HLA) class II molecules and single nucleotide polymorphisms (SNPs) with OA caused by various agents (isocyanates, red cedar, acid anhydrides, platinum salts, natural rubber latex, laboratory animals).[65] Recent Korean studies have suggested that genetic factors may also be important in the development of work-related respiratory symptoms and sensitisation to wheat flour in bakery workers. Cho *et al.*[66] found that toll-like receptor 4 (TLR4) gene polymorphisms are associated with allergic sensitisation to wheat flour. While Hur *et al.*[67] reported that genetic polymorphisms of β_2-adrenergic receptors (ADRB2) may contribute to the development of work-related symptoms in workers exposed to wheat flour, leading to baker's asthma.

ATOPY

It is estimated that 20-35% of the population are affected by atopy associated with allergic disease, with about 60% of asthmatics being atopic.[68] Studies investigating OA among bakers have reported a positive correlation between atopy and the development of sensitisation and asthma.[69,70] A recent study among bakers and pastry makers, also reported atopy as being an independent risk factor for OA.[71] Results from exposure-response studies suggest that atopy is an important modifier of sensitisation in bakery workers, as evidenced by having a more pronounced exposure-response relationship compared with non-atopic bakers.[62]

AGE

The effect of age on the development of asthma has been inconsistent. Studies of new-onset asthma among adults suggests that the risk decreases with advancing age.[72,73] However, advancing age has been shown to increase the risk of OA among farmers.[74] A review on occupational allergy and asthma among bakery workers, suggests that age does not appear to be associated with sensitisation or work-related respiratory symptoms.[14]

GENDER

Gender has not been shown to be associated with sensitisation or work-related symptoms among bakery workers.[14] It has been postulated that the increased risk of OA associated with gender can be ascribed to the gendered distribution of work.[65] This has been shown in studies of asthma and occupational exposures to cleaning agents, which clearly demonstrate an increased risk among females since they are more likely to be exposed to various cleaning agents than men.[75]

SMOKING

Smoking has been shown in some studies to increase the risk of sensitisation in bakery workers exposed to flour.[16,76] However, while one study showed an increased risk of sensitisation in bakery workers,[16] others have demonstrated that smoking does not appear to increase the risk of asthma.[15,62] It can be regarded as an inconsistent risk factor for baker's allergy and asthma.

PREVENTION STRATEGIES FOR REDUCING FLOUR-DUST EXPOSURE AND BAKER'S ASTHMA

Exposure-response relationship studies for wheat allergen exposure suggest that reducing the exposure to flour-dust allergens is likely to reduce the burden of allergic respiratory disease. Results from various studies demonstrate evidence of a direct relationship between OA and exposure to airborne allergens.[59] Furthermore, these studies have shown that the intensity of exposure to sensitising agents is the most important risk factor for OA. Primary prevention strategies aimed at reducing workplace exposure to sensitising agents would be the most rational approach for reducing the burden of OA.[77] The exposure-response relationship studies for wheat allergen exposure described earlier suggest that reduction of allergen exposure levels may reduce the number of sensitised bakery workers.[62] However, despite the overwhelming evidence that workplace exposures to flour dust should be controlled, prevention strategies in bakeries appear not to have been very satisfactory. While various countries have proposed exposure limits for flour dust, some are not totally protective and minimal action beyond general requirements has been applied.[78]

REGULATORY EXPOSURE STANDARDS

In the absence of specific regulatory exposure standards for allergens of biological origin in South Africa, the Regulations for Hazardous Chemical Substances (HCS) promulgated under the Occupational Health and Safety Act (OHSA) require regular environmental monitoring and medical surveillance of workers at high risk of developing adverse health effects associated with exposure to respiratory sensitisers.[79,80] Under these regulations grain dust is defined as 'dust arising from harvesting, drying, handling, storage or processing of barley, wheat, oats, maize, rye, including contaminants'. Grain dust has been designated an exposure control limit of 10 mg/m^3 TWA (total inhalable dust) and is denoted as a sensitiser (exposure should be prevented especially activities giving rise to short-term peak concentrations). In addition to this permitted level being much higher than international standards, the allergenicity of unmilled grain is different to milled grain used to produce flour, and the standard is therefore not appropriate for bakeries.

The high sensitisation potential of flour dust makes the South African grain standard inadequate for protecting the health of bakery workers. Cullinan *et al.*[15] showed strong relationships between exposure to flour dust and health endpoints such as sensitisation and various work-related symptoms. These endpoints were observed at flour dust levels well below 10 mg/m^3. Should the exposure levels not be considerably reduced to below 10 mg/m^3 OEL (occupational exposure limit) sensitisation, work-related respiratory symptoms, asthma and rhinitis are still likely to occur, based on the epidemiological evidence.[81] This points to the need for specific exposure limits in South Africa aimed at flour-dust allergens such as wheat, rye and α-amylase.

The American Conference of Government Industrial Hygienists (ACGIH) have adopted a threshold limit value (TLV) of 0.5 mg/m^3 and in Holland the Dutch Expert Committee of the Health Council adopted a grain dust limit of 1.5 mg/m^3.[81-83]

WORKPLACE INTERVENTIONS

Prevention of OA related to a work-sensitising agent is best achieved at the workplace through primary prevention measures such as avoidance, or reduction of the occupational exposures.[84] Exposure reduction is crucial as it is estimated that approximately one-third of workers with OA are unemployed up to 6 years after diagnosis.[85, 86] There is evidence suggesting that reduction in exposure leads to reduction in disease burden.[87, 88] While there have been some notable successes in reducing OA, especially due to latex, in healthcare workers,[89] several studies however indicate that there has been no decrease in exposure to flour-dust allergens in the last decade.[90, 91] Several dose-response studies indicate that in some cases exposure levels will need to be reduced 10-fold or more to have a significant impact on sensitisation and respiratory health effects associated with flour and enzymes.[20,62]

As total avoidance is not possible in bakeries, exposure reduction is the preferred approach. However, there are few well-designed systematic intervention studies with detailed exposure characterisation data to determine the effect of exposure reduction in the occupational exposure levels. In addition little is known about the changes in incidence and prevalence of OA over time.[92] Studies that describe the effectiveness of control measures specifically in bakeries are few. Since only a limited number of exposure reduction measures have been studied in practice, little is therefore known about the effectiveness and efficacy of many exposure reduction measures.[93]

Recently, some new data are emerging on the effectiveness of various interventions and control measures in bakeries.[94,95] Although the data demonstrate varying degrees of effectiveness, these studies do provide insight into their potential to reduce exposure in bakeries.[87] It has been demonstrated that local ventilation concentrated to flour release points, such as weighing stations, dough-making machines, dough brakes, and bread machines, can reduce dust exposures to concentrations below 1 mg/m^3.[12] A large-scale Dutch study showed that control measures that were introduced during weighing of ingredients, especially by limiting the use of bagged flour products and the enclosure of silos (when dumping flour), significantly decrease exposure.[95] Other investigators have suggested that automation of parts of the process is a long-term option that may lead to considerably lower levels of exposure.[96]

A systematic review (2012) of the effectiveness of general occupational health and safety (OHS) *training* confirms that such training promotes safer work practices among workers and recommends that workplaces continue to deliver OHS training as part of a larger risk-management programme. It cautions however that training alone will not necessarily prevent injuries and illnesses.[97] Fishwick and colleagues also demonstrated the relevance of *education* in reducing workers' exposures.[98] In this study a significantly higher level of work-related symptoms and work-related specific IgE was observed in those who received no training (12% vs 1%, $p<0.001$).[98] A sector-wide intervention programme in Dutch bakeries aimed primarily at education of workers showed a rather limited effect on exposure levels.[91] The authors concluded that although workers' knowledge about the risk of flour-dust exposure improved, the change in work practices was rather limited. Overall, this information suggests that the use of appropriate knowledge and effective flour-dust control measures, coupled with training and supervision, has the potential to reduce flour-dust exposures in bakeries.

Certain *work practices* to avoid flour dust becoming airborne have also been suggested such as careful bag emptying and bag handling, and the use of vacuums instead of pressurised air for cleaning activities. During the dough-making process, a major source of wheat exposure occurs when dough is covered with flour, to prevent it sticking to work surfaces. It has been shown that for specific products a *change in work practice* such as the use of divider oil could reduce exposures (Fig. 2). Studies by Burstyn *et al.*[99,100] demonstrated a 28-fold decrease in flour-dust exposure when substituting dusting flour with divider oil, while Meijster *et al.*[95] reported a rather modest reduction in exposure when substitutes like divider oil and dust-free flour were used.

Very few studies have demonstrated the effectiveness of *personal protective equipment* in respect of reducing exposure to high allergen loads in general and flour dust in particular. The use of respiratory protective equipment can only offer protection when it is worn properly, removed safely and either replaced or maintained regularly. A recent review on the primary prevention of OA reported several examples of indirect evidence that use of respiratory protective devices may prevent asthma onset, by demonstrating that respirators can reduce exposure to agents that can cause OA.[93] The first case study report on flour dust and two patients with OA concluded that dust respirators were effective in preventing asthmatic reactions induced by buckwheat and wheat flour.[101] In a later study on wheat-allergen exposure investigators compared exposure levels measured inside a P2 particle filter facemask with measurements taken outside the facemask. In this study, the authors demonstrated that exposures were reduced by 93-96% when these facemasks were used, and concluded that these respirators may help to prevent baker's asthma.[102] Nevertheless many studies have shown that personal protective equipment, although very effective in some cases, is especially vulnerable to wrong and ineffective use, and should therefore only be used as a last resort for exposure reductions in cases where all other options are not possible.


Fig. 2. Example of activity to reduce airborne flour dust exposures using divider oil (left) instead of flour (right) to prevent adhesion of dough to work surface.

SURVEILLANCE

ENVIRONMENTAL EXPOSURE LEVEL MONITORING

Environmental exposures need to be adequately monitored to assess effectiveness of interventions. Monitoring of dust as opposed to allergen levels has its limitations in that dust levels may only partially correlate with the actual allergen concentrations. Furthermore, as has been suggested it is questionable whether dust levels are a valid exposure parameter in occupations where IgE-mediated allergies predominate. Studies show that the correlation between concentrations of dust and wheat allergen is moderate, but poor for fungal α-amylase.[13]

MEDICAL SURVEILLANCE

Medical surveillance aims to detect OA in workers at an early stage and to remove those sensitised before the allergic respiratory disease becomes severe or irreversible.[103] The most widely used methods for medical screening and surveillance of occupational allergic respiratory disease are questionnaires, immunological tests and spirometry.[84] The use of skin-prick test and specific IgE for workers exposed to flour allergens has been shown to have a high predictive value in individuals who have subsequently developed asthma.[103]

However, the effectiveness of medical surveillance in the baking industry (or in any other field of OA) has not been systematically evaluated. A study by Gordon *et al.*[104] among bakery workers showed that workers who reported respiratory symptoms in a screening questionnaire were no more likely to have asthma (or OA) than those who responded negatively. Furthermore, a study among supermarket bakery workers that compared an independent cross-sectional survey with a routine in-house company surveillance programme suggested that health surveillance can underestimate the burden of OA by a factor of 4-7.[105]

A recent review on the benefits of medical screening, reported on new approaches to medical surveillance that are based on developing diagnostic models to enable the prediction of the probability of sensitisation in workers exposed to high-molecular-weight allergens.[106] These models use questionnaire-based predictions that enable risk stratification of workers and allow for identifying workers requiring further clinical evaluation. Two studies among bakery workers have demonstrated that simple short questionnaires, developed to predict flour sensitisation, can accurately identify those at risk of developing work-related allergic respiratory disease.[107, 108]

CONCLUSION

In conclusion, it is evident that despite the high prevalence of baker's allergy and asthma in certain high-risk working populations, further research needs to focus on characterising the specific asthma phenotypes and their prevalence in bakery workers. While baker's allergy and asthma is well described, investigations into the extent to which occupational exposure to various allergens constituted a risk to the health of bakery workers in supermarkets are limited.

Characterising the complex interactions between environmental factors and individual susceptibility is a crucial step in identifying the factors that determine the development of baker's allergy and asthma. Environmental determination of bakery allergens is an essential aspect of demonstrating exposure-response relationships. While the nature of exposure response relationships has been investigated to some extent, the clinical endpoints have focused primarily on allergic sensitisation and work-related symptoms, rather than baker's asthma, which is the most disabling of outcomes. Further exploration is needed of factors that attenuate or enhance exposure-response relationships, such as host susceptibility, other environmental cofactors, such as endotoxins and chemical pollutants, gene-environment interactions and the role of other pathophysiological mechanisms that may underlie these responses.

Finally, to arrive at an accurate estimate of the impact of interventions, studies are needed that allow for the detailed evaluation of the impact of specific interventions if implemented on their own or in a multifaceted manner to reduce the exposure to flour dust in those at risk. Future studies also need to evaluate the long-term and sustained impact of exposure reductions on reducing associated allergic respiratory disease among bakery workers, which may best be achieved through cohort studies.

Declaration of conflict of interest
The authors declare no conflict of interest.

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