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The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

120. Flour Dust

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Nordic Council of Ministers

ARBETE OCH HÄLSA VETENSKAPLIG SKRIFTSERIE

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Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an expert group. At present the Nordic Expert Group consists of the following member:

Vidir Kristjansson	National Board of Occupational Health, Iceland
Petter Kristensen	National Institute of Occupational Health, Norway
Per Lundberg (chairman)	National Institute for Working Life, Sweden
Vesa Riihimäki	Institute of Occupational Health, Finland
Adolf Schaich Fries	National Institute of Occupational Health, Denmark

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as Toxline, Medline, Cancerlit and Nioshtic. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access are used. The draft document is discussed within the Expert Group and is finally accepted as the Group's document.

Editorial work is performed by the Group's Scientific Secretary, Gregory Moore, at the National Institute for Working Life in Sweden.

Only literature judged as reliable and relevant for the discussion is referred to in this document. Concentrations in air are given in mg/m^3 and in biological media in mol/l. In case they are otherwise given in the original papers they are if possible recalculated and the original values are given within brackets.

The documents aim at establishing a dose-response / dose-effect relationship and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on Flour dust was made by Drs Ulla Tiikkainen, Kyösti Louhelainen and Henrik Nordman at the Finnish Institute of Occupational Health. The final version was accepted by the Nordic Expert Group 14th May, 1996, as its document. The authors and Expert Group thank Dr Jonas Brisman for informed comments on this document.

Gregory Moore
Scientific Secretary

Per Lundberg
Chairman

Abbreviations

ACGIH	=	American Conference of Governmental and Industrial Hygienists
AM	=	Aritmetic mean
BMRC	=	British Medical Research Council
CEN	=	European Committee for Standardization
D_{ad}	=	aerodynamic diameter
EC	=	European Community
FEV_1	=	Forced expiratory volume in one second
GM	=	Geometric mean
IOM	=	Institute of Occupational Medicine, Edinburgh
ISO	=	International Organization for Standardization
LOAEL	=	Lowest Observable Adverse Effect Level
Mini-Ram	=	Mini- Respirable Aerosol Monitor
MRI-device	=	A bench-scale, impact-type chamber to measure the dustiness of a variety of finely divided solid materials (Midwest Research Institute, Kansas City USA)
NOAEL	=	No Observable Adverse Effect Level
OEL	=	Occupational exposure limit
PEFR	=	Peak expiratory flow rate
PNOC	=	Particulates not otherwise classified (ACGIH)
PNSE	=	Particulates with no specific effect
SPT	=	Skin prick test
STEL	=	Short term exposure limit
TWA	=	Time-weighted average

Contents

1. Introduction

Flour dust in bakeries and flour mills is a well-known occupational health problem world-wide. The principal manifestations of allergy are asthma, rhino-conjunctivitis or dermatitis. Although flour dust as a cause of disease has been recognised for centuries (32, 41, 104) preventive actions have been insufficient to control sensitisation. Despite modern techniques, sensitisation and work-related symptoms are common even in modern bakeries and mills and flour dust is still one of the most common cause of occupational respiratory allergy in many countries (24, 56, 78, 128).

Total dust measurements in workplace air are often used to estimate the flour dust exposure. Occupational exposure limit (OEL) values (8-hour time-weighted averages) for organic dust vary between 3-15 mg/m^3 (Appendix 1). So far no country has set OELs based on the sensitising property of flour dust.

This document summarises the recent literature on flour dust exposure in bakeries and mills. It focuses on the allergens identified in flour, on flour exposure levels, and prevalences and incidences of flour-induced diseases in relation to exposure levels. The non-cereal allergens occurring together with flours are also discussed.

Because the pathogenesis of diseases caused by grain dust differs from flour-induced disorders, grain dust exposure was considered beyond the scope of this document. The health hazards of grain dust have been reviewed in this series by Brown (25).

2. Substance Identification

Flour dust consists mostly of cereal flours from different cultivars and millings of wheat (*Triticum*) and rye (*Secale*). To a lesser extent barley, oats, rice and maize flours are used. Besides its cereal components, flour dust may contain several non-cereal antigens such as buckwheat and soybean flour, storage mites and moulds. The bakery dust consists also of several additives which are frequently used in the baking process: so-called dough improvers may contain enzymes of fungal or bacterial origin. Spices, sugar, egg and milk powders may also be part of the airborne flour (Table 1).

Table 1. The content of flour dust and some of its components.

Content of flour dust	Components
Cereal flours	Flour glycoproteins, starch
Mites	Dermatophagoides, Lepidoglyphus, Tyrophagus, Glycyphagus, Acarus and Blomia
Fungi	Penicillium, Aspergillus and Alternaria species
Insects	Granary weevil, rice flour beetle
Enzymes	Malt enzymes, α-amylase, protease, cellulase, hemicellulases, xylanase, glucoamylase, glucose oxidase
Chemicals as flour ingredients	Preservatives (e.g. sorbic acid, acetic acid), bleaching agents (e.g. benzoyl peroxide, potassium bromate), antioxidants (e.g. ascorbic acid, lauryl and propyl gallate). emulsifying agents, vitamins
Other additives	Baker's yeast, soybean flour, soybean lecitin, egg powder, sugar
Flavourings and spices	Anis, cardamom, cinnamon, cloves, ginger, laurel, lemon, nutmeg, peppermint, vanilla

3. Characteristics of Flour Dust

3.1 Physical and chemical properties

The range of flour particle size is wide, the smallest particles being less than 1 μm and the largest about 200 μm in diameter (55). Using IOM dust spectrometer (designed by Institute of Occupational Medicine, Edinburgh) a biomodal distribution of aerodynamic diameters (D_{ad}) of flour dust were shown by Lillienberg and Brisman (68). The smallest particles were around 5 μm, and the bigger ones around 15-30 μm. The substantial proportion of flour dust is large particles; over 50% of particles have D_{ad} over 15 μm.

In microscopic studies flour can be seen to consist primarily of two components, protein and starch. The protein contents of whole wheat and wheat flour are nearly equal (12% vs. 11%) (55) and in airborne flour dust the similar protein content is measured, being about 10% (26, 70). The smaller flour particles are composed of protein or small starch granules with adhering proteins, and as particle size increases, a large proportion of free starch granules is obtained and the protein content becomes lower; so particles under 17 μm tend to be high in protein with a protein content much higher than in the original flour (55, 62).

Typical wheat has an ash (mineral) content of about 1.5%. However, the ash is not distributed evenly in the grain, and the ash content of flour is 0.4% (55). In airborne bakery dust the organic content has been close to 100% (138).

3.2. Characterisation of allergens

3.2.1. Flour

Several allergenic components of flour have been identified. Osborne (94) defined fractions of flour proteins according to their solubility in various solutions. Water-soluble albumin and globulin fractions of wheat flour have been shown to contain most of the allergens involved in bakers' allergies, whereas gliadins extracted with aqueous alcohols and glutenins soluble in dilute acid are considered less allergenic (8, 136). Blands et al. (17), using crossed immunoelectrophoresis (CIE), found 40 antigenic fractions in flour extract; IgE of wheat flour allergic patients revealed affinity to 18 of them demonstrated by crossed radioimmunoelectrophoresis (CRIE). Recently patients with baker's asthma have been demonstrated to have specific IgE also to wheat gliadins (116).

Taxonomically related flours share common proteins but they also possess unique components of their own (2, 42). Also cultivars of the same species may have slightly differing components (137).

The molecular weights of identified flour allergens vary between 12-64 kDa (40, 99, 117). The major allergens (about 15 kDa) of flours belong to the group of the α-amylase inhibitors (10, 39, 44) which prevent insect α-amylases from harming the cereal. The glycosylated forms of these proteins have been suggested to be the most potent allergens (77, 113).

Three isoforms of wheat profilins are produced by cDNA cloning and since their structure resembles other plant profilins known as allergens it is assumed that wheat profilin may be one of the relevant allergens in flour hypersensitivity (107).

Cereal (barley) α- and β-amylases, with a molecular weight of 54 kDa and 64 kDa, respectively, are also allergens and cross-reactivity between α- and β-amylases was shown by RAST inhibition. On the contrary low cross-reactivity was found between the barley amylases and fungal α-amylase (117). Wheat flour has been analysed to contain cereal α-amylases 0.1-1.0 mg/g flour (26, 60).

3.2.2. Non-cereal allergens

In addition to cereal allergens, flour dust may also contain other allergic components like storage mites, fungi, enzymes, and spices but the identification of their allergens is mainly limited to the molecular weight determination of IgE binding components.

The most thoroughly examined are the allergens of a mite *Lepidoglyphus destructor (L. destructor)* with a 14 kDa major allergen named Lep d I ((46)). *Tyrophagus putrescentiae (T. putrescentiae)* mite bodies and faeces have been

shown to contain 20 antigens and 5 allergens; the main IgE binding component being 16 kDa (61). Strong allergenic cross-reactivity between storage mites *L. destructor, Acarus siro (A. siro)* and *T. putrescentiae* is shown by the immunoblotting inhibition technique, and cross-reactivity between house-dust-mite, *Dermatophagoides pteronyssinus (D. pteronyssinus)*, and storage mites also occurs (61). The main allergens of *D. pteronyssinus* are the cysteine proteases Der p I (25 kDa) and Der pII (15 kDa) which are also thought to be an enzyme (125).

Airborne fungi and insects can be present in flour dust. The molecular weights of the allergens in *Aspergillus fumigatus* and *Alternaria alternata* range from 18-90 kDa (64). Moreover, allergens of the granary weevil (*Sitophilus granarius*) and rice flour beetle (*Tribolium confusum*) have been demonstrated (51, 119).

Allergens from the enzymes used in dough improvers are also identified. The purified allergen of *Aspergillus oryzae* α-amylase, Asp o II (11), has a molecular weight of 54 kDa. Cellulase has been demonstrated to contain several IgE binding components larger than 40 kDa (103).

Other additives used in bakeries and confectionaries are different kinds of spices and flavourings. Their allergenic components are proteins or chemicals, such as cinnamon compounds. In soybean flour extract nine proteins with molecular weights ranging from 15-54 kDa were found to be allergens by immunoblotting (27). Purified enolase (52 kDa) was shown to be an major allergenic component of baker's yeast extract (6).

Table 2. Major occupations and sites involving flour dust.

Workplace	Work task/occupation
Mills	Milling, packing, cleaning, maintenance
Bakeries	Mixing, dough preparation, bread preparation, cleaning
Confectioneries	Weighing, mixing, production
Pasta and pizza bakeries	Production
Animal feed plants	Mixing
Malt factories	Drying, sieving, packing
Agriculture	Milling, feeding

Table 3a. The number of bakeries (establishments) accorrding to the number of workers. Data from the manufacturing statistics of Statistics Denmark, Finland, Iceland, Norway and Sweden. 1,581 = production of soft/fresh bread (not crisp bread, biscuits, etc.)

Branch	Country	Number of workers:							
		<5	5-9	10-19	20-49	50-99	>100	Total Bakeries	Total Workers
		Number of bakeries:							
1581	Denmark	669	376	174	29	7	6	1,305*	17,200
1581	Finland	717	117	104	84	28	10	1,060	9,800
	Iceland							106	840
1581	Norway	204	151	107	64	10	6	542	6,300
1581	Sweden	908	251	127	73	29	17	1,405	12,300

* incl. 44 bakeries of unknown size

4. Occurrence, Production and Use

Although the main flour exposure occurs in bakeries and mills, flours are used in several other industries. Table 2 shows the sites and occupations representing the major flour dust exposure.

For the baking industry it is typical that small companies, often family enterprises, dominate the branch. For instance in Finland 700 out of 1000 bakery enterprises employ less than 5 persons. This is similar in the other Nordic countries. Table 3a shows the sizes of bakery establishments and numbers of bakery employees in the Nordic countries.

Bakery work comprises of several different job titles and work tasks. The most common are doughmakers, bread-formers, oven workers, confectionary workers, packers, slicers, bakery maintenance or cleaning staff and mixed or miscellaneous tasks. Especially in smaller enterprises it is common to move from one task to another.

As with the bakeries, mills can also be divided into small and large industrial sites. Typical work tasks for a miller are grain receiving and handling, milling, sacking or bagging. In addition, in larger mills special cleaning staff and laboratory workers are employed. Table 3b shows the number of mills and employees in the Nordic countries.

According to the manufacturing data of Statistics Denmark, Finland, and Sweden the total amount goods produced by baking industry (bakeries and bread factories over 5 employees) are about 300,000 tons per year whereof over 60% is soft bread. The quantity of flour used in bakeries varies considerably depending on size and production style. Values from 50 kg flour/day up to 55,000 kg/day are mentioned (70).

Table 3b. The number of mills and employees according to Statistics Denmark, Finland, Norway and Sweden. Branch 1561 = mill product industry

Branch	Country	Mills	Employees
1561	Denmark	25	904
1561	Finland	97	574
1561	Norway	100	769
1561	Sweden	144	785

From the 1970s sugar degrading enzymes have been used as dough improvers in the baking industry. According to the enzyme activity analyses and the manufacturers' information, dough improvers contain 0.2-1% enzyme (22, 60) and the improver itself is only about 1% of the dough. Up to now the vast majority of enzyme preparations have been used in powder form. Less dusty forms such as granulated or liquid preparations have been introduced onto the market.

The most often used enzyme in the baking industry is α-amylase of *Aspergillus oryzae (A. oryzae)*. Other fungal enzymes including proteases, cellulases and xylanases, are used to a lesser extent (12, 22, 130). Although enzyme preparations are often named according to the main enzyme activity, many other enzymes may be present in the same preparation. The use of industrial enzymes has been reviewed in this series by Brisman (21).

Common genera of storage mites are *Lepidoglyphus, Tyrophagus, Glycyphagus, Acarus* and *Blomia*. Exposure to storage mites is a risk factor for inhalant allergy especially in rural workers, but storage mites can cause problems in other occupations such as bakers and grain store workers (46). Also considerably amounts of *Dermatophagoides* allergens were detected in dust samples from Spanish bakeries (23-42% of total mites) (9).

5. Measurements and Analysis of Workplace Exposure

5.1 Analysis of total, inhalable and respirable dust

The definitions of inhalable and respirable dust have been discussed since the first proposals of the BMRC (British Medical Research Council) in the 1960s. During the past ten years also ACGIH (American Conference of Governmental and Industrial Hygienists) and ISO/CEN (International Organisation for Standardisation/European Committee for Standardisation) have published methods concerning size-selective sampling devices.

The EC-countries have adopted a standard which defines three categories of conventions for size-selective sampling (34). An inhalable fraction is a fraction of airborne particles inhaled through the nose and mouth. The thoracic fraction is a

fraction of inhaled particles penetrating beyond the larynx, and a respirable fraction is one penetrating to the unciliated airways. The work of defining and specifying the sampling devices fulfilling the requirements of the standard is ongoing. Up to now several different filters and samplers have been used for flour dust sampling which makes it difficult to interpret dust measurements. For example, Lillienberg and Brisman (68) found that there was a linear correlation between the IOM sampler and the traditional Millipore cassette, but the IOM collects almost twice as much flour dust as the conventional total dust sampler.

Personal sampling should generally be emphasised because it determines the exposure of different individuals or task groups. Stationary sampling gives usually lower dust concentrations than personal sampling and reflects the general area situation and is suitable for preventive measures. Most of the results are expressed as arithmetic means (AM) with a standard deviation and range. The distributions of total dust are often log-normal, and geometric means (GM) and deviations should be used.

The filters used are made of glass microfibre, cellulose acetate membrane or polytetrafluroethylene with a diameter of 25, 37 or 45 mm (5, 26, 37, 43, 57, 58, 60, 83, 89, 90, 138).

The traditional method of measuring total dust is sampling the dust onto preweighed open- or close-faced casettes with a portable pump and determination of the amount of dust by weighing (5, 35, 37, 43, 60, 83). As a standardised method it may be applied for both stationary sampling and personal sampling. The sampling efficiency for particles above 10 µm with open face filter holder is low as a result of low inlet sampling velocity.

The most recent instrument for sampling inhalable dust is the IOM inhalable dust sampler which was developed to follow the criteria for inhalable dust. It has a 50% cut-off D_{ad} of about 50 µm. This enables the collection of the inhalable fractions of airborne dust in many environments (73), including bakeries (26, 68). Besides IOM-sampler other personal samplers connected to various sampling heads have been used for inhalable flour dust collection (58, 89).

To measure respirable dust fractions size-selective heads have been used (35, 37, 89, 115). In addition, the devices used for analysing respirable particles are cyclones (43, 138) and the Hexhlet two-stage dust sampler, which is also used for total dust sampling (4, 14, 143).

5.2 Analysis of size distribution

For the analysis of size distribution of airborne bakery dust the IOM personal inhalable aerosol spectrometer has been used (26, 68). It is an eight-stage impactor with a backing filter. The inlet has a 50% cut-off D_{ad} of 50 µm as does the IOM sampler. The eight-stage Sierra Marple personal cascade impactor with the glycerol-coated mylar membranes has also been used to collect flour dust samples for size distribution analysis (114).

5.3 Flour aeroallergen measurements

Immunoinhibition assays with pooled human flour-specific IgE (123) and IgG4 (58) or flour-specific antisera from immunised rabbits (115) are used to estimate the concentration of flour allergens/antigens in flour dust.

The antigens identified by the rabbit IgG and human IgG4 are compared to the allergens recognised by the specific IgE from humans, and were shown to have molecular weights similar to those of flour allergens. No cross-reactivity was observed with non-cereal antigens such as fungal α-amylase. The standard curves were made with mixed flour extract (123), Canadian Western Red Spring (CWRS) wholemeal extract (115) and wheat flour antigen preparation (58). The detection limits for wheat flour antigens were 1 µg/ml (115) and 20 ng/ml meaning approximately 50 ng/m^3 (58).

Although valuable data have been obtained from flour aeroallergen measurements, the problem of general standardisation remains. The flour aeroallergen assays are difficult to make comparable between laboratories.

5.4 Enzyme analysis

The amounts of α-amylase in the flour dust in bakeries were measured with the catalytic activity methods (26, 60, 130). For the standardisation, Fungamyl 1600S (Novo, Denmark) and Roberts α-amylase (Puratos Inc., Belgium) were used. The detection limits for α-amylase were 0.02 µg/ml (60) and 0.1 µg/filter (26) which resulted in detection limits of approximately 0.01-10.0 µg/mg of inhalable dust depending on the filter load.

The determination of fungal α-amylase concentration in air samples has also been conducted with the sandwich enzyme immunoassay with affinity purified polyclonal rabbit anti-α-amylase antibodies. The detection limit was 250 pg/m^3 and Fungamyl 1600S was used as standard (57).

The cellulase (detection limit 20 ng/m^3) and xylanase (detection limit 2 ng/m^3) contents of the air samples were determined with specific antibodies using the dot-blot technique (130).

6. Occupational Exposure and Uptake

Numerous research reports have been published on the frequencies of disorders and immunological responses in workers exposed to flour dust. Only few reports give exact data on dust exposure. Some reports may only have one measurement representing the whole exposure pattern of the workers in a particular bakery or mill. Lately, however, a series of reports has been published on the measurements of flour dust and aeroallergen (flour proteins) concentrations (37, 38, 56, 87, 89, 90, 115, 123). Also the size distributions of flour dust (37, 68, 114, 143) and enzyme concentrations, mainly α-amylase in bakeries and mills, have been described (21, 57, 130).

6.1 Flour dust exposure

Tables 4 and 5 summarise the results of flour dust measurements in bakeries and flour mills. Only work tasks involving exposure to flour dust have been included from the mill environments.

The wide concentration range of flour dust is a common feature to the studies referred. In the first stages of the baking process, the mean concentrations during normal whole shift work have usually been higher than in the later phases of the process (Table 4a), and the levels are equal to or exceed the most common recommended OELs of 3 or 5 mg/m^3 in the Nordic countries (see Appendix 1).

Among the highest means of total dust measurements, 10 mg/m^3 (AM, n = 28), have been recorded in dough preparation in the bakeries (70) and 11 mg/m^3 (GM, n = 2) at the ingredient preparation site in the confectionery bakery (83). The maximal concentrations are usually as much as 6-fold compared to OELs, but e.g. Bohadana et al. (20), measured up to 100 mg/m^3 at "a special baker". However, no details were given concerning that particular work task.

In mills, high concentrations of total dust have been measured during laboratory milling (70), packing (37, 70), packing with shovelling (5), sifting (37), and cleaning (90). The range of results has been as large as in the bakeries.

Very little information is available on the dustiness of bakery or mill materials. Heinonen and Enbom (48) measured dustiness of several wheat and rye flour brands, and also of a dough improver with a MRI-dustiness device (29). The device is a bench-scale, impact-type chamber for measuring the dustiness of finely divided solid materials (Midwest Research Institute, Kansas City USA). The lowest dustiness index was found with wheat flour (index 1-6 mg/kg flour), followed by rye (index 4-9 mg/kg flour) and flour additive (index 65 mg/kg material). The index describes the mass of less than 18 µm D_{ad} dust originating from flours.

Dust reduction or dust control in bakeries or mills has seldom been reported in the literature. The concentration of total dust was reduced dramatically during the weighing of flour additives in a laboratory experiment (48, 49). With only general ventilation, the mean concentration of total dust was 45 mg/m^3. The lowest concentration measured was 0.06 mg/m^3 when the general ventilation, local exhaust and also local supply air systems were on in the test room.

The effect of local ventilation exhaust hoods on dust exposure during mixing and dough preparation work in bakeries has also been studied by Heinonen and Enbom (48). Exhaust hoods were installed over dough bins and automatic portioning machines. The concentration of total dust decreased by 66%, and the concentration of total dust in the workers' breathing zone was below 3 mg/m^3. In addition, peak concentrations before intervention had been several hundreds mg/m^3; these were reduced to 10%.

Table 4a. Concentrations of flour dust in bakeries, personal sampling

Task/occupation	n	Concentration of dust, mg/m^3					Sampling	Ref.
		AM	SD	GM	GSD	Range	device	
1. Weighing of flour,	7	4.2	1.6			2.3 - 6.5	1	60
mixing, dispensing	24	9.0		5.0	2.5	1.4 - 86.0	3	89
2. Dough preparation	28	10.2	14.1			1.0 - 75.0	1	70
- " -	6	7.4	5.4				2	68
- " -	7	8.4				3.0 - 18.8	1	130
- " -	34	6.9		5.5	2.1	1.2 - 16.9	2	26
- " -	13	4.6	3.6			0.9 - 14.7	1	60
- " -	-			12.0			4	114
- " - and bread preparation	11	12.6	9.2			1.0 - 25.9	1	70
- " - small bakery	40	2.9	2.4			0.2 - 12.4	1	138
- " - large bakery	28	14.3	25.9			0.6 - 113	1	138
- " - large bakery	105			3.0		0.4 - 37.7	6	58
- " - and cleaning	12			2.1		0.1 - 16.8	1	83
3. Bread preparation	35	6.4	5.2			1.0 - 22.5	1	70
- " -	6	8.0	6.7				2	68
- " -	10	3.2				1.2 - 5.5	1	130
- " -	62	3.4		2.7	2.0	0.6 - 14.2	2	26
- " -	7	2.3	0.9			1.5 - 3.4	1	60
- " -	45	1.6		0.9	2.9	0.1 - 16.0	3	89
- " - small bakery	69	1.7	1.2			0.3 - 7.6	1	138
- " - small bakery	36			3.3		1.2 - 8.8	6	58
- " - large bakery	3	3.3	1.9			1.1 - 4.5	1	138
- " - rye bread	9	7.5	7.0			1.2 - 19.0	1	70
- " -	4	3.4	3.7			0.7 - 8.7	1	20
- " - special bread baking	5	41.3	39.5			10.0 - 98.0	1	20
4. Roll production	32	3.6		2.4	2.5	0.4 - 21.1	3	89
- " -	5	3.1	1.8			0.5 - 5.2	1	70
	5			1.9			4	114
5. Pastry preparation	11	2.8	2.0			0.7 - 6.2	1	70
6. Croissant preparation	4	0.7	0.2			0.5 - 0.9	1	20
scone production	7			6.6		1.8 - 13.0	1	83
7. Oven worker	8	2.4	2.2			0.5 - 7.4	1	70
- " -	10	1.6		1.2	2.4	0.2 - 4.0	2	26
- " -	6	1.1	0.9			0.5 - 2.7	1	20
- " -	16			1.7		0.0 - 37.6	1	83
- " - small bakery	12	1.1	0.6			0.2 - 2,4	1	138
- " - large bakery	2	1.7	0.5			1.4 - 2.0	1	138
- " - large bakery	81			0.6		0.1 - 5.1	6	58
Oven control	3	3.2	1.7				2	68
8. Packing	23			0.3		0.0 - 3.7	1	83
- " -	31	0.5		0.4	1.7	0.2 - 1.8	3	89
- " -	15	1.5	1.2			0.5 - 4.3	1	70
- " - and slicers, transport	132			0.4		0.1 - 2.8	6	58

Table 4a. (Contd.)

Task/occupation	n	Concentration of dust, mg/m^3					Sampling	Ref.
		AM	SD	GM	GSD	Range	device	
9. Cleaning/hygiene	36	2.6		1.7	2.6	0.2 - 12.9	3	89
"	27			0.7		0.3 - 5.5	6	58
10. Others								
Production managers	20			0.6		0.1 - 4.9	6	58
All round staff	66			0.9		0.9 - 26.8		58
Machineman, large bakery	17	1.0					1	138
CONFECTIONARY								
Ingredient preparation	2			11.0		10.0 - 12.0	1	83
Weighing of additives	6	4.4	2.7	3.7	1.9	1.6 - 8.8	1	74
Dough production	3	3.9	3.4	3.0	2.3	1.7 - 7.8	1	74
Pastry rolling	9	2.3	1.2	2.0	1.8	0.7 - 4.2	1	74
Dough prod., mixing	10			2.7		0.6 - 14.1	1	83
Dough production	9	7.5		6.4	1.8	2.9 - 15.3	3	89
Confectionary	19	2.3	3.6			0.5 - 15.6	1	70
Confectionary worker	7	0.9		0.6	2.6	0.2 - 3.0	2	26
-"-	22			0.7		0.1 - 3.7	6	58
Work with						30.0 - 95.5	5	143
flour, sugar, talc, starch	-							
almonds, cocoa, cacao	-					20.0 - 35.6	5	143
honey, yeast, additives	-					4.1 - 12.4	5	143

AM = arithmetic mean, SD = standard deviation, GM = geometric mean, GSD = geometric standard deviation
Sampling devices: 1 = membrane filters in a filter holder, diam. 25, 37, 45 mm, 2 = IOM sampler, 3 = Seven-hole sampler (Casella); 4 = 8 stage cascade sampler (Sierra); 5 = horizontal two stage sampler (Hexlett);
6 = PAS-6 sampling heads

6.2 Peak exposures

Short term exposures to high concentration of flour dust are known to be frequent in bakeries. Although there is no univocal consensus as regards to duration of peak exposures these denote mostly exposure periods of about from 30 seconds to 4 minutes. In addition to such peak exposures there may be operations associated with high concentrations for up to half an hour. These contribute to time-weighted averages (TWA) and may be essential in the progress of sensitisation. However, they should probably not be called peak exposures.

Peak flour exposures and short-term tasks in bakeries and mills were identified and total dust and aeroallergen levels measured (90). The frequency of the work tasks varied usually from 1 to 16 per shift, and the duration from 2 minutes to 4 hours. The latter time period should regarded as long-term measurement period.

Table 4b. Concentrations of flour dust in bakeries, stationary sampling

Task/occupation	n	Concentration of dust, mg/m^3			Sampling	Reference
		AM	SD	Range	device	
2. Dough preparation	39	3.8	4.3	0.4 - 17.0	1	70
- " -	9	2.5		0.7 - 8.4	1	130
- " -	12	4.3	4.5	0.8 - 14.2	1	60
3. Bread preparation	17	1.2	1.2	0.1 - 4.4	1	70
- " -	11	1.1		0.1 - 2.9	1	130
- " -	5	1.2	1.1	0.4 - 4.2	1	60
- " -	9	2.2	3.8	0.1 - 11.7	1	70
4. Roll production	8	7.5	9.8	1.0 - 29.9	1	70
5. Pastry preparation	3	0.8	0.6		1	70
8. Packing	16	0.3	0.2	0.1 - 1.0	1	70
- " -	1	0.1			1	130
CONFECTIONARY	15	0.4	0.2	0.1 - 0.9	1	70

AM = arithmetic mean, SD = standard deviation, GM = geometric mean, GSD = geometric standard deviation

Sampling devices: 1 = membrane filters in a filter holder, diam. 25, 37, 45 mm

The exposure concentrations for the tasks were often much higher than the average levels measured over a shift. For example, in bread production, the geometric mean of peak exposure (9 mg/m^3) measured for 30 minutes was 10-fold compared to the geometric mean of the whole shift measurement (0.9 mg/m^3) (88). During cleaning work the geometric mean of the whole shift was 1.7 mg/m^3 whereas short-term peak concentrations varied from 29.8 mg/m^3 to 42.9 mg/m^3. The highest concentration of total dust (390 mg/m^3) was measured in cleaning the bins in bakeries, and in maintenance cleaning in mills (458 mg/m^3) (90).

The flour aeroallergen concentrations followed the pattern of the total dust concentrations between short-term peak exposures and over-a-shift exposures (90). The highest concentrations in both the bakeries and mills were measured during cleaning operations. In the bakeries, the GM for cleaning bins was 1,139 µg/m^3 (n = 5), and for maintenance cleaning in mills 3,606 µg/m^3 (n = 3). The corresponding GM values over a shift in hygienic tasks were 73-149 µg/m^3 in the bakeries and 134-1,728 µg/m^3 in the mills (89, 90)

In a Finnish study (60), the weighing of additives lasted from 10 to 40 minutes. The mean concentration of total dust during the weighing of additives (4.2 ± 1.6 mg/m^3, mean ± S.D.) did not differ from that measured during the entire shift of dough preparation (4.6 ± 3.6 mg/m^3).

Lillienberg and Brisman (69) examined the peak exposure concentrations of flour and frequency of peaks in dough makers and bread formers using a Mini-

RAM (Respirable Aerosol Monitor) with a light emitting source and scattered electromagnetic radiation detector. The Mini-RAM gives relative dust concentrations and for calibration, parallel sampling with IOM-sampler was used with the integration time period set at 1 min. The peak exposure concentrations were found to be higher for dough makers compared to bread formers. Tipping flour, mixing dough and manual handling of flour were the dustiest tasks where concentrations varied from a few mg/m^3 up to 100 mg/m^3. The duration of the peaks were 3-4 min and 2-6 peaks per hour were recorded (Figure 1).

The Mini-RAM aerosol photometer (model PDM3) was used also with the PIMEX (Picture, Mix and Exposure) -method (109) for real time monitoring in Finnish bakeries (48). The response of the Mini-RAM was calibrated in the bakeries to correspond the breathing zone total dust concentration using the parallel sampling with open-faced Millipore 37 filter casette. The integration time period of the response was 2 seconds in oder to simulate the inhalation time. During the measuring periods several high concentration peaks in the breathing zone were recorded with a maximum of 850 mg/m^3 during flour tipping in dough making without local exhaust (Figure 2). The mean breathing zone total dust concentration was 26 mg/m^3 during the whole period.

6.3 Inhalable and respirable dust

The reported amounts of inhalable and respirable dust of the flour dust are based on various collecting devices and definitions (see Section 5.1. "Analysis of total, inhalable and respirable dust").

In a Sudanese flour mill the means of concentrations of respirable airborne dust (D_{ad}) <7 µm, Hexhlet sampler) varied between 0.3 and 0.9 mg/m^3 in the different parts of the mill. The respiratory fractions were 23-31% of the total dust concentrations (4).

Fonn et al. (37), reported mean concentrations of respirable dust from 0.6-1.1 mg/m^3 in the breathing zone at sites where flour dust was prominent in a mill. The respirable fraction of the total dust varied from 11% at very high exposure sites to 38% at low exposure sites.

In a study of confectionery workers, stationary samples were collected (Hexhlet two-stage sampler). The mean concentration of respirable dust was 2.0 mg/m^3, which was 6% of the mean total dust concentration. The respirable dust concentrations were 3-5.4 mg/m^3 in a group of confectionery workers who handled flour, sugar, talc, starch; 1.5-3.2 mg/m^3 in a group handling nuts, almonds, cocoa, cacao and chocolate, and the lowest 0.3-1.7 mg/m^3 in a group handling butter, honey, yeast and colour additives (143).

Respirable fractions (D_{ad} <5 µm) were collected in breathing zone during the bagging of flour, cleaning of sifters, and pre-slinging in a Parisian mill. The concentration of respirable particles was less than 0.4 mg/m^3 and below 3% of inhalable fractions. The inhalable fractions were relatively high, from 5-54 mg/m^3 (43).

Table 5a. Concentrations of flour dust in mills, personal samples.

Task/occupation	n	Concentration of dust, mg/m^3					Sampling device	Ref.
		AM	SD	GM	GSD	Range		
1. Milling								
- " - large mill	17	2.9	3.6			0.5 - 15.9	1	70
- " - small mill	16	28.6	51.3			2.2 - 202	1	70
- " -	2	3.8				2.5 - 5.1	1	37
- " -	12	3.0		2.4	1.9	1.0 - 9.4	3	89
- " -packing, supervision	4	1.3				0.4 - 2.4	1	5
2. Sieving								
- " -	-	3.6	1.6				5	4
- " -	2	8.6				7.8 - 9.3	1	37
3. Rolling								
- " -	-	2.2	1.1				5	4
4. Mixing								
- " -	2	5.0				3.3 - 6.7	1	130
- " -	12	13.8		11.0	2.0	3.0 - 36.7	3	89
5. Laboratory								
-sifting, grinding	4	17.2		11.7	2.6	4.4 - 45.0	3	90
-milling	5	8.1	12.4			1.0 - 30.1	1	70
-lab work	4	1.5	1.2			0.7 - 2.8	1	70
	1	1.8					1	130
6. Packing, < 10 kg sacks								
- " -	3+3	4.8 - 17.7[1]				2.7 - 31.2	1	37
- " -	-	1.6	0.8				5	4
- " -	2	7.8	3.3	7.4	1.6	5.4 - 10.1	1	43
- " -	-			15.3			4	114
- " -	10	6.5	8.6			0.6 - 24.5	1	70
- " - small mill	3	33.7	16.1			22.3 - 45.1	1	70
- " - shoveling	13	17.6				0.8 - 95.6	1	5
- " -	48	8.3		5.7	2.2	1.8 - 71.0	3	89
- " - bag handling	11	3.5				0.6 - 8.7	1	5
7. Sacking,> 10 kg sacks								
- " - large mill	14	4.2	3.6			0.5 - 22.7	1	70
- " - small mill	13	34.7	49.6			5.4 - 193	1	70
8. Cleaning								
- " -mill	6	2.4	1.4			0.5 - 2.4	1	70
- " -		3.5				0.4 - 7.7	1	5
- " - sifters	2	40.8		36.6		27.6 - 53.9	1	43

AM = arithmetic mean, SD = standard deviation, GM = geometric mean, GSD = geometric standard deviation 1 measured on two separate packing floors
Sampling devices: 1 = membrane filters in a filter holder, diam. 25, 37, 45 mm; 2 = IOM sampler; 3 = Seven-hole sampler Casella; 4 = 8 stage cascade sampler Sierra; 5 = horizontal two stage sampler Hexlett

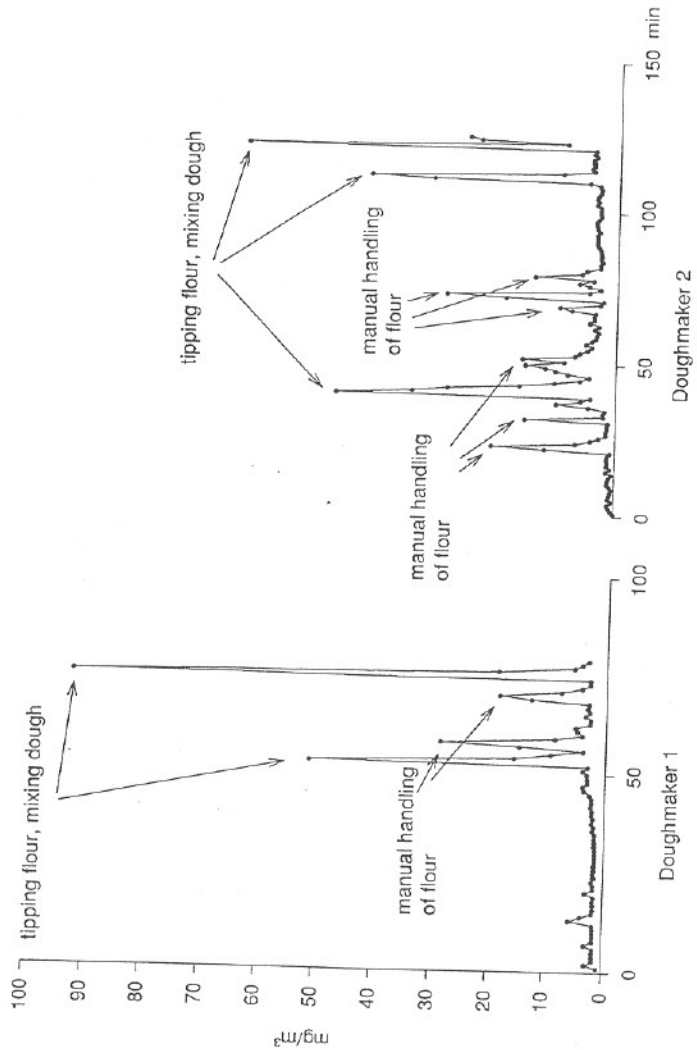

Figure 1. Continuos measuring of flour dust exposure in dough makers with the Mini-RAM with parallel sampling using an IOM-sampler. The integration time period was set at one min. Figure reproduced with permission from Lillienberg & Brisman (69).

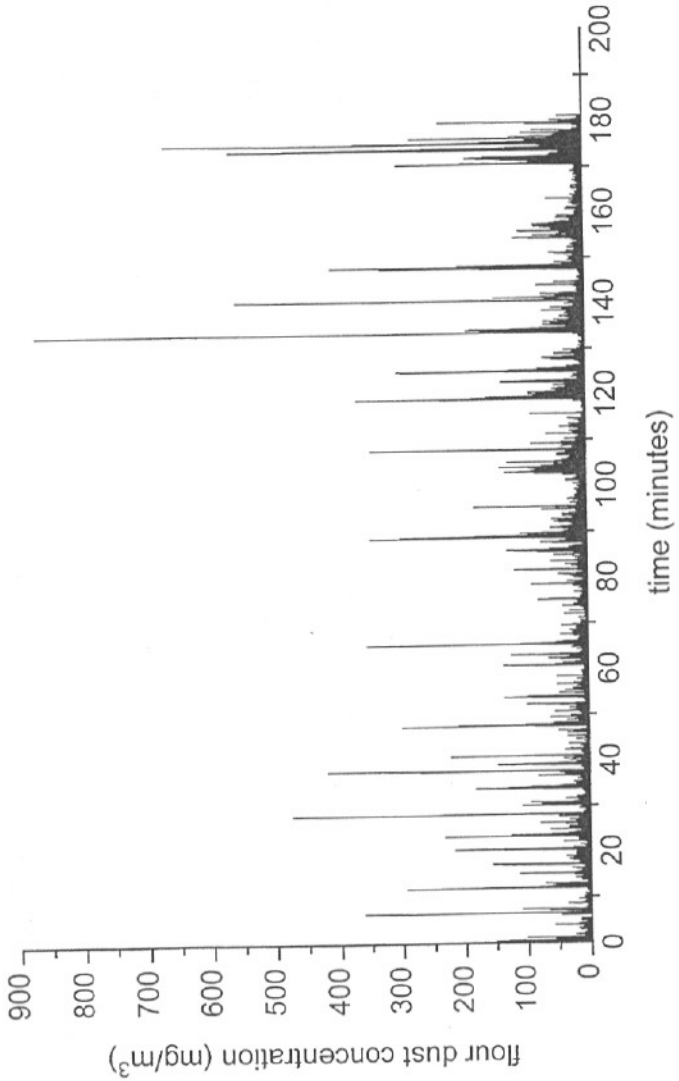

Figure 2. The variation of dust concentration in dough maker's breathing zone monitored by a Mini-RAM with parallel sampling using a open-faced Millipore 37 filter cassette. The integration time period of the response was two seconds. The bakery was small and the weighing area was equiped with a hood without exhaust ventilation. Figure reproduced with permission from Heinonen & Enbom (48).

Table 5b. Concentrations of flour dust in mills, stationary samples.

Task/occupation	n	Concentration of dust, mg/m^3			Sampling device	Ref.
		AM	SD	Range		
1. Milling						
- " - office	5	0.1	0.1	0.1 - 0.2	1	37
2. Sieving						
- " - large mill	9	0.4	0.5	0.1 - 1.3	1	70
- " - small mill	6	5.6	5.3	0.2 - 13.3	1	70
- " -	2	1.7		1.5 - 2.0	1	37
3. Rolling						
- " - large mill	6	0.6	0.5	0.1 - 1.4	1	70
- " - small mill	14	7.6	12.4	0.7 - 49.3	1	70
4. Mixing	4	1.0		0.7 - 1.3	1	130
5. Laboratory	1	0.3			1	130
6. Packing						
- " -	2+2	7.6 - 17.0[1]		4.6 - 29.3	1	37
- " -	8	3.6	1.9	0.3 - 5.8	1	70
7. Sacking.						
- " - large mill	5	4.8	4.4	0.6 - 12.9	1	70

AM = arithmetic mean, SD = standard deviation, GM = geometric mean, GSD = geometric standard deviation

1 measured on two separate packing floors

Sampling devices: 1 = membrane filters in a filter holder, diam. 25, 37, 45 mm

In Danish bakeries the fractions of respirable dust were 27% and 21% of the total dust in small and large (factory) bakeries, respectively (138). Stationary sampling with cyclones was used.

Using IOM personal inhalable dust samplers in Swedish bakeries, Burdorf et al. (26) estimated that the thoracic fraction was 39% and the respirable fraction 19% of the flour dust. Lillienberg and Brisman (68) also used an IOM sampler in four different work tasks in bakeries and flour mixing factories, and reported the percentages of thoracic and respirable dusts according to the ACGIH and BMRC definitions, respectively. The dustiest task was mixing of dough with 14.1 mg/m^3 of inhalable dust, whereof the thoracic fraction was 26% and the respirable fraction 9%. The lowest inhalable dust concentration was measured along the oven control, with 75% of thoracic and 45% of the respirable fractions.

Fakhri (35) measured extremely high concentrations of respirable dust in two Sudanese mills because of the insufficient ventilation. For sieving, storage and packing the mean concentrations were 23 mg/m^3, 23 mg/m^3 and 95 mg/m^3, respectively.

6.4 Aeroallergens

The measurements of specific flour antigens (flour protein) have rarely been carried out, and because of the different methods and standardisation, the results cannot be directly compared. The terms aeroallergen, wheat antigens or airborne flour allergens are used as in the original publications to refer to the flour protein components measured in flour dust.

Tee et al. (123) determined airborne flour in 55 personal samples from British bakeries. They observed that the concentration of airborne flour allergens was related to the gravimetric measurement of total dust. In 56% of the samples ranked in the high flour exposure category, the flour allergen content was over 10 µg/m^3, whereas only in 1 of the 32 samples with the low exposure rank that limit was exceeded.

Nieuwenhuijsen et al (89) had analysed 488 air samples for flour aeroallergens from British bakeries and mills. Variations in aeroallergen concentrations were observed in the different exposure groups. The comparison with total dust and aeroallergen concentrations showed that exposure in the different areas of the bakeries depended on the use of products other than flour. The relation between total dust and amounts of flour aeroallergens was not observed in the mixing areas; low in the confectionery areas; the highest for hygiene workers. In general, the concentrations of flour aeroallergens increased linearly with increased total dust concentrations, and the total dust concentrations varied more than the aeroallergen concentrations between different groups.

In a Dutch study on 21 bakeries, 449 air samples of wheat flour antigen levels were determined (58). The highest concentration of wheat antigens was measured at wheat bread production sites for dough makers, and the lowest for oven staff at rye bread production sites. The ratio of flour antigen concentration and inhalable dust levels were used to estimate the differences in wheat antigen exposure compared to inhalable dust. The exposure differences between the workers were greater for wheat antigens concentrations than for flour dust in large bakeries, but hardly any differences in antigen /dust ratio was found between job titles in small bakeries. It was also noted that wheat antigen concentrations could be measured even in samples where inhalable dust could not be detected.

To determine the size of allergen-bearing particles in the air, stationary samplers and the competitive inhibition radioimmunoassay method were used (114). In the dusty dough-brake area in a bakery and in the packing area of a mill, about 70% of the particles were between 14.8 - 21.3 µm in diameter; 10% were under 6 µm. In a less dusty roll production area about 50% of the flour particles to which the workers were exposed were below 6 µm in diameter. The authors conclude that in dusty areas most of the flour particles are deposited in the nasal passages and upper airways and a smaller proportion, 8-20%, is deposited in the bronchial airways and alveoli.

Table 6 shows the concentrations of flour aeroallergens in different tasks in the bakeries.

Table 6. Concentration of wheat flour protein or flour aeroallergen in bakeries and in mills, µg/m^3.

Task/occupation	n	Concentration µg/m^3 AM	GM	GSD	Range	Reference
BAKERIES						
Dough preparation	9	387	208	3	36 - 1910	89
Mixing	24	310	229	2	26 - 842	
Roll production	32	260	215	2	71 - 1020	
Cleaning inside	36	410	149	4	15 - 4500	
Confectionary/flour	26	327	252	2	63 - 1160	
Maintenance	22	170	121	2	44 - 587	
Bread production	45	241	177	2.3	44 - 744	
Roll wrapping	24	141	101	2.3	29 - 512	
Bread wrapping	31	57	46	2.0	8 - 257	
Confectionary/no flour	33	102	80	1.9	38 - 383	
MILLS						
Flour mill	12	341	248	2.3	69 - 950	
Wheat mill	4	167	154	1.6	78 - 234	
Mixing	12	406	303	2.0	135 - 1740	
Packing	48	304	227	2.2	46 - 971	
Hygiene	4	137	134	1.3	109 - 190	
Maintenance	7	230	186	3.3	28 - 1064	
BAKERIES						
Dough preparation, large bakeries	76		5.3		0.03 - 252	58
Maintanance cleaning	27		0.2		0.03 - 2.6	
Bread production small bakeries	31		6.0		1.3 - 53	
Oven staff, large bakeries	71		0.3		0.03 - 68	

6.5 Enzymes

Since the publishing of Industrial enzymes in this series (21) a couple of studies on measurements of airborne enzymes in bakeries have come out.

α-amylase allergen concentrations were measured in personal dust samples, using the sandwich enzyme immunoassay. In all, 480 dust samples were analysed, and α-amylase was detected in 92 samples. The levels of α-amylase exposure varied considerably, depending on job title and type of bakery. The workers were classified into three different exposure groups: low (n = 7, GM = 0.7 ng/m^3, range 0.2-8.8 ng/m^3), medium (n = 43, GM = 1.3 ng/m^3, range 0.2-33.2 ng/m^3) and high (n = 27, GM = 18.1 ng/m^3, range 0.2-221.8 ng/m^3). The dough makers were the most heavily exposed group with the highest measured α-amylase exposure of 222 ng/m^3 (57).

In a study of four bakeries, one flour mill and a crisp bread factory, the air concentrations of α-amylase, cellulase and xylanase at the different work sites were determined (130). Both personal and stationary samples was taken. The α-amylase concentrations followed the total dust concentrations. In the bakeries the α-amylase levels in the breathing zone were the highest in dough making, and ranged from <0.2 μg/m³ to 6.6 μg/m³ (n = 7) but were below 0.4 μg/m³ in bread making (n = 10). In the mill the α-amylase concentration in the breathing zone was comparable to that of dough making in bakeries (n = 2, range 0.7-1.1 μg/m³). In the samples (n = 10) from the crisp bread factory, the α-amylase levels were <0.4 μg/m³.

The cellulase and xylanase air samples were collected by stationary samplers. No cellulase, but air concentrations of 1-200 ng/m³ xylanase were found in the bakeries (n = 10). In the flour mill the cellulase concentrations (n = 3) varied between 65-180 ng/m³ at the site where additives were mixed, being highest during active mixing; the xylanase levels ranged from 2-5 ng/m³. In the crisp bread factory the comparable levels of cellulase (n = 4) were measured in different phases of mixing, dough making and bread forming as at the additive mixing site in the flour mill. The concentrations of xylanase were higher in the crisp bread factory (range 7-40 ng/m³) than in the flour mill.

6.6 Task-based grouping of flour exposure

It is important to divide workers into uniformly exposed groups when studying exposure-response relationships between flour dust exposure and work-related symptoms or skin sensitivity. Overlap in exposure groups, great variability in the workers' exposure and random biases can lead to under- or overestimation of the exposure-response effect. Especially in smaller enterprises it is common for bakery and mill workers to move from one task to another, and this makes it difficult to estimate the true exposure levels of workers in different task groups. However, some studies have been conducted to find optimal grouping strategies to study flour dust exposure. The variability of flour exposure within and between workers and work tasks have been investigated (26, 56, 88).

In the survey of Burdorf et al. (26) inhalable dust samples from 13 bakeries were collected. The work task was found to be the main factor affecting differences in flour exposure of bakery workers. There was a hierarchy in mean exposure of the task groups: the most heavily exposed were dough makers, then bread-formers, oven workers, confectionery workers, and finally packers. From the repeated measurements it was concluded that among bread-formers and packers the within-worker variance was an important factor influencing the total exposure variability, whereas among dough-makers the between-worker variance was greater than within-worker variance. The conditions specific to a bakery explained only 9% of the workers' flour exposure variability, and the size of the bakery did not contribute significantly at all.

Nieuwenhuijsen et al. (88) examined exposure variability in flour mills and bakeries using 13 different exposure groups. The levels of fluor dust were measured in the mixing and packing areas in flour mills and packing stations, and the dispense/mixing area and dough brake in the bakeries. The between-worker variation was smaller in the various exposure groups than in the whole population. The exposure group component was responsible for more than half of the total exposure variability. The changes in daily exposure explain a part of the variability, which emphasizes the importance to sample sufficient times to get precise estimation of exposure. In addition, between-worker variation was great in roll production and confectionery tasks. The different bakeries (n = 3) or mills (n = 2) had only a small effect on variation.

Grouping factors influencing the exposure estimates of inhalable dust, wheat aeroallergen and α-amylase were examined by Houba (56) in 5 large and 16 small bakeries. Large bakeries were distinguished according to the production type, and the workers were divided into 6 occupational groups. In smaller bakeries workers were divided into three groups according to their work tasks. The highest concentrations of inhalable dust were found for dough makers in large bakeries and for bakers involved in bread production in the small bakeries. The specific job of a bakery worker was the most important factor of variability in inhalable flour dust and wheat allergen concentrations, but the type of bakery explained some of the variability as well. For α-amylase allergen exposure the type of bakery was more important than job information in those bakeries where α-amylase concentration could be measured.

7. Toxicokinetics

The deposition and elimination of flour dust follow the patterns of other solid aerosols of similar particle type. The size, density, shape and aerodynamic properties of flour dust particles and the volume of respiration determine particle deposition in the lungs (96).

Substantial amount of flour dust particles are over 10 μm in diameter (68, 114) and therefore they remain in the upper respiratory tract. In the alveolar region of the respiratory tract, maximum particle deposition is seen to lie in the 2 μm to 5 μm range of particle diameter (96).

Macrophages and the mucociliary system are responsible for the clearance of flour particles from the lungs. However, under heavy exposure the ability of macrophages to eliminate particles is exceeded, and dust particles may penetrate into the interstitium. The individual characteristics of an exposed person are also of great importance in the development of disease (96).

8. Biological Monitoring

No method is commonly available for biological monitoring of the flour exposure. The occurrence of specific IgG antibodies in serum has been suggested to reflect exposure (45, 127, 141). The determination of specific IgE antibodies in serum or skin prick test with flour extract is sometimes used to follow sensitisation or the development of allergic disease.

9. Mechanisms of Toxicity

9.1 Immunological reactions

Allergic rhinitis, conjunctivitis, asthma, urticaria and protein contact dermatitis are the immunologically mediated clinical manifestations caused by exposure to flours or other proteinaceous bakery allergens.

The primary sensitisation of the airways occurs through the participation of denritic cells which line the bronchi both in the epithelium and in the submucosa. Denritic cells have the capacity to identify, process and present antigen to T-lymphocytes which recognise processed antigens. Further differentiation of T-cells along the Th2-type pathway involves the upregulation of several interleukins, e.g. interleukin-4 (IL-4) and interleukin-13 (IL-13) (54). Besides the presence of IL-4 and IL-13 physical interaction between Th2-cells and B-cells is required for the synthesis and regulation of IgE antibody production; thus human IgE production results from collaboration between Th2-cells and B-cells (108).

Once sensitised to specific allergens subsequent exposure results in allergic symptoms. The immediate symptoms are mediated through the cross linkage of IgE-receptor on the mast cells by specific allergen resulting in release of mediators: histamine, prostaglandins and leukotrienes. These mediators account for allergic reactions: damage to epithelium, swelling, mucus secretion and contraction of airway smooth muscle (54).

Specific IgG_4 antibodies to flours have also been detected in bakers' sera but the role of IgG_4 antibodies in the sensitisation process is not clear (101, 126). In addition to immediate reactions, delayed asthmatic responses to wheat and rye flour have also been reported (50).

Contact urticaria and protein contact dermatitis (53) are due to the large protein molecules contained in the materials to which bakers are exposed; among them are flour, enzymes, spices, egg proteins and storage mites. Also the terms atopic contact dermatitis or baker's eczema are used (100, 139). As with respiratory allergies specific IgE antibodies can elicit an immediate wheal and flare skin reaction, and specific IgE antibodies can be identified directly from the serum (66). According to some authors protein contact dermatitis may also be a result of delayed type cell-mediated allergic reactions (122).

Delayed type allergic contact dermatitis is usually caused by small chemicals, haptens, which are bound to proteins in vivo. The skin reactivity is caused by allergen-specific T-cells which have been activated by antigen presenting Lagerhans cells (111).

Moulds and related mycotoxins which can be included to bakers' allergens are capable of producing both specific IgE antibodies and immune complex-mediated hypersensitivity (64).

9.2 Non-immunological reactions

Less than a half of the flour-related respiratory symptoms have been demonstrated to be due to immunological reactions, and therefore a part of the bakers' bronchial symptoms as well as rhinitis or conjunctivitis are thought to have a non-allergic basis (30, 56, 121). Similarly a local immediate urticarial reaction can also be of non-immunologic origin and irritant contact dermatitis is caused by physico-chemical properties such as moisture, acidity, heat or mechanical irritation (111).

10. Effects in Animals and in Vitro Studies

No data are available.

11. Observations in Man

In several cross-sectional studies, work-related symptoms have been reported to occur in 6 to 30% of flour-exposed workers (30, 35, 56, 110, 121, 142). The annual incidence of occupational respiratory allergies in bakers is high in many countries, however, due to differences in reporting systems of work related diseases data from different countries are not totally comparable. For example, Finland has a register on occupational diseases based on compulsory reporting of occupational diseases by physicians (78) whereas the Swedish register is based on cases reported for workers' compensation from the social security system (24). Compared with two voluntary reporting systems in England, occupational respiratory diseases are reported 3-5 times more frequently in Finland (78).

Table 7 shows the annually reported respiratory allergies and skin diseases of the bakers and pastry makers to the registers of work-related diseases in Denmark, Finland and Sweden. The Norwegian Register of work-related diseases notified that during 1985 to 1995, 45 bakers or confectioners were reported to have developed a respiratory disease (allergic or non-allergic) and 39 bakers or confectioners had allergic or irritation eczema.

Table 7. The number of respiratory allergies and skin diseases in bakers and pastry makers reported as occupational. Data are from the registers of the Danish Working Environment Service; the Finnish Register of Occupational Diseases and from the registers of the National Board of Occupational Safety and Health, Sweden. It should be noted that each country has its own reporting system and thus the values are not comparable. The proportion of bakers respiratory allergies and skin diseases out of all reported occupational respiratory allergies and skin diseases is given in parenthesis.

Year	Respiratory allergies			Skin diseases		
	Denmark	Finland	Sweden	Denmark	Finland	Sweden
1992	55 (10.4%)	65 (8.0%)	36 (5.4%)	49 (2.4%)	23 (2.0%)	16 (1.2%)
1993	41 (9.5%)	61 (7.1%)	26 (1.9%)*	70 (3.7%)	14 1.2%	14 (0.6%)*
1994	50 (10.2%)	65 (7.4%)	12 (4.3%)	60 (3.6%)	21 (1.7%)	6 (0.9%)

* The Swedish values for 1993 are not quite comparable with other years, as in 1993 there was a change in the Work Insurance Act, and consequent intense campaigns to report occupational injuries.

11.1 Effects on respiratory tract

11.1.1. Flour

Flour proteins are the main cause of bakers' allergies and several studies on the pathogenesis of baker's rhinitis and asthma have been conducted. Skin prick-tests (SPT) and bronchial provocation tests have been used. Serum IgE antibodies from diseased bakers recognised components from wheat, rye and barley flours, and the determination of flour-specific IgE antibodies were found useful in the diagnosis of allergy to inhaled wheat flour dust (15, 17, 18). Skin test reactivity with flours and flour-specific IgE antibodies showed a good correlation (15).

Herxheimer (52) investigated bakers and baker apprentices with a relatively short flour exposure. After a few weeks of exposure 9% of the apprentices had positive flour SPT reactions, but half of them became SPT negative during their first 12 months in the trade. At the end of the third working year, however, the total number of flour-positive apprentices rose to 19% and health complaints due to flour increased from 0.2% to 7% at the end of the third year. A considerable drop out of apprentices obscures the result; 290 apprentices were examined out of originally 880 persons after three years and only 37 after five years.

Thiel and Ulmer (124) performed a study among 85 baker apprentices, 29 randomly selected apparently healthy male bakers and 38 bakers with diagnosed occupational disease. The controls were 60 male students from vocational schools and 29 male administration employees. Five per cent of the baker apprentices whose exposure time varied between one and three years complained of work-related rhinitis. In a group of randomly selected bakers 21% had flour-related

complaints; the exposure time before the onset of symptoms was between 7 and 32 years.

In 5% of the baker apprentices, 21% of the randomly selected bakers, and 91% of the diseased bakers, the intracutaneous skin test to flours was positive. In both control groups only one person had a positive skin test to wheat flour. Specific IgE to wheat flour was found in 13% of the apprentices (in 17% of the vocational student controls), whereas 28% of the randomly selected bakers had wheat-specific IgE, and up to 80% of the bakers with occupational disease were wheat IgE-positive. Similarly increased frequencies of positivity were noted in the acetylcholine test. Twenty-two per cent of the baker apprentices, (8% of the controls) had bronchial hyperreactivity, 46% of the randomly selected bakers and 84% of the diseased bakers. Of the adult male controls, 17% had a positive reaction in the acetylcholine test. One of the apprentices had a positive bronchial provocation test with wheat and rye flours. Of the randomly selected bakers, 10% had a positive reaction to wheat and 17% to rye, and of the diseased bakers, 61% were wheat and 71% rye positives in bronchial provocation.

Since the late 1980s several extensive studies have investigated flour sensitisation in bakers and millers. In an Australian survey 176 male bakers and 24 bread slicers and wrappers were examined (102). The bakers had a greater prevalence of attacks of wheezing and breathlessness than did the slicers and wrappers (20% vs. 4%). Twenty (11%) of the bakers fulfilled the criteria of work-related asthma. The asthmatic bakers had more frequently increased bronchial hyperreactivity (PD20 <30 µmol) (75% vs. 37%) and positive SPT to wheat flour (50% vs. 10%) and common allergens (35% vs. 12-19%) than the other bakers. The bakers who reacted to wheat on SPT had a significantly greater prevalence of seasonal rhinitis and co-existing positive SPT responses to common allergens than the bakers who did not react to wheat. A positive relationship between the duration of baking and the frequency of positive SPT to wheat antigens was observed. A group of oven handlers (n = 16) had a higher prevalence of attacks of wheezing and breathlessness, and their standardised FEV_1 (forced expiratory volume in one second) was significantly lower compared to the general bakers and dough makers.

In a survey of 226 Italian bakers and pastry makers, work-related asthma was reported by 4.9% and rhinoconjuctivitis by 17.7% of the employees; 10.2% of the workers suffered from chronic bronchitis. Skin prick-tests to wheat flour was positive in 12%, and to common allergens in 24% of the workers. Skin sensitisation to occupational allergens (flours and storage mites) was significantly associated with atopy ($p < 0.001$), smoking ($p = 0.015$) and years as baker ($p = 0.027$). The risk of work-related symptoms was associated with sensitisation to wheat, α-amylase, storage mites and with atopy (142).

Houba et al. (56) studied 393 bakery workers. Wheat allergens and fungal α-amylase, were measured in 449 and 507 personal inhalable dust samples of workers, respectively. Atopicity was defined as elevated total IgE or presence of specific IgE to common allergens and sensitisation was determined as detectable amount of specific serum IgE.

Twenty-three per cent of the bakers reported work-related symptoms; however, only 30% of the symptomatic workers were sensitised to either wheat or α-amylase. Wheat flour specific IgE was detected in 10% and 7% had IgE to fungal α-amylase; 2% were sensitised to both.

Bakers were divided in three different wheat allergen exposure groups (low GM = 0.1 μg/m^3; medium GM = 0.7 μg/m^3; high GM = 3.8 μg/m^3) based on their total job histories. The exposure-response relationship between wheat allergen exposure and wheat specific IgE sensitization was observed in atopic and non-atopic individuals being strongest in atopics. The relationship between wheat allergen exposure and respiratory symptoms was analysed with multiple regression analysis. The prevalence of work-related symptoms increased in groups of higher exposure levels. The relationship was stronger among those who were sensitised than among non-sensitised. Prevalence rate ratios among sensitised were 2.4 (1.4 in non-sensitised) in medium exposure group and 2.7 (1.6 in non-sensitised) in high exposure group. The lowest exposure group as a control group had a prevalence rate ratio 1.0 and the atopics 2.7. Similarly exposure-response relationships were described between α-amylase exposure groups and amount of specific IgE sensitised and work-related symptoms.

Five persons suffering from occupational laryngitis with immediate allergy caused by flours (wheat, rye or buckwheat) have been diagnosed (112). Work-related allergic laryngitis is a seldom diagnosed symptom. All the cases were confirmed with provocation tests in which the patients displayed a change in vocal cord status. Positive SPT reactions as well as specific IgE to causative flour were demonstrated. Besides allergic laryngitis all patients had flour induced rhinitis and some of them suffered also from asthma, dermatitis or pharyngitis.

Recently a retrospective cohort investigation using self-administered postal questionnaires was conducted among Swedish bakers (n = 2,923) to estimate the asthma incidence rate and the risk to develop asthma compared to unexposed referents (24). The incidence rate (cases per 1,000 person-years) for asthma among male bakers was higher, 3.0, than in male referents (0.9-1.9). Also the relative risk of male bakers to develop asthma during baker work was increased 1.8 (95% confidence interval 1.3-2.6) compared with a combined comparison group of referents. Among female bakers no higher asthma incidence for asthma was noted compared to referent groups. Persons who ever had worked as a baker reported significantly more frequently that they had changed job because of asthma (2.5%) than referents(1.1%).

In order to establish dose-response relationships, each baker was assigned an estimate of current and cumulative flour dust exposure (23). Exposure levels were based on inhalable dust measurements in a random sample of Swedish bakeries (n = 12) (26). Three exposure levels were distinguished (1, 3 and 6 mg/m^3) which corresponded to certain bakery work tasks asked for in the questionnaire. Cumulative flour exposure estimates were calculated by multiplying the time spent in each work task with the corresponding exposure level. Incidence rate for asthma in male bakers increased by increasing cumulative dust dose being 3.4 cases/1000

person years with a cumulative dust dose of >30 mg years/m^3 compared to 1.2 of unexposed. Incidence rate for rhinitis increased 2-3 fold in all current exposure classes compared to unexposed indicating the dependence of current exposure and onset of rhinitis.

The studies containing health data and measurements of flour dust exposure in bakeries and mills are dealt with in Section 12, "Dose-Effect and Dose-Response Relationships".

11.1.2. Cross-reactivity

The cross-reactivity of specific IgE may indicate that persons once sensitised to an allergen are likely to develop hypersensitivity to other components sharing similar or closely related antigens. Several studies have shown cross-reactivity of IgE antibodies to different cereal flours. The specificity of IgE antibodies from flour allergic patients was found to be directed not only against common flours (wheat, rye) but also against other taxonomically related cereals. Using RAST inhibition, the degree of cross-reactivity of the tested sera of asthmatic bakers followed closely the taxonomic relationship of cereals in order: wheat, triticale, rye, barley, oats, rice and corn (7, 19, 118). Using western blotting, allergens of the same molecular weight have been recognised in wheat, rye and barley flours by sera of hypersensitive persons (42, 118, 131); also soybean flour has been demonstrated to contain some allergens which are identified by the sera of wheat flour allergic bakers (118).

11.1.3. Enzymes

Allergies due to enzymes in bakeries have been reported since 1986 when Baur et al. demonstrated the role of *Aspergillus* α-amylase in baker's asthma (12). The document on Industrial enzymes by Brisman (21) summarises the respiratory health effects also of non-proteolytic enzymes (mainly α-amylase). Since then some new data on bakers' enzyme allergies have been published.

Moneo et al. (80) examined the sensitivity to fungal α-amylase among 259 millers without any known occupational contact to α-amylase or any other enzyme. Ocular, nasal and respiratory symptoms were reported by 28% of the workers. Six per cent of the millers had positive SPT to α-amylase, 3% had specific IgE (5 symptomatic, 2 asymptomatic) and 17% had specific IgG to α-amylase. The correlation between positive SPT and the presence of symptoms was significant. Positive SPT to α-amylase and α-amylase specific IgE and IgG antibodies were also associated with positive skin tests to common allergens. The authors conclude that although cross-reactions with environmental allergens cannot be totally excluded as the reason for α-amylase sensitisation in millers, grain or flours can be contaminated by *Aspergillus* and other moulds which secrete amylases to which the workers are then sensitised.

In a subsequent report 25 asthmatic subjects with suspected α-amylase hypersensitivity and 10 unexposed controls were studied by SPT, a capture ELISA for

IgE, immunoblotting and bronchial provocation tests. Eight patients showed a positive bronchial provocation to α-amylase and seven of them had also positive SPT to α-amylase and six had specific IgE. However, four more bakers had positive SPT to amylase but no reaction in bronchial provocation nor specific IgE were demonstrated. It was concluded that SPT alone is a sensitive but unspecific tool for the diagnosis of symptomatic α-amylase allergy in bakers (81).

In a Dutch study (57) of 178 bakery workers 25% had work-related symptoms. As many as 9% had positive SPT to fungal α-amylase compared to 2% of laboratory animal workers and 8% had α-amylase specific IgE. 15% of the workers had positive SPT to occupational allergens, including wheat and rye flours, α-amylase and baker's yeast. In the whole examined group α-amylase sensitisation increased from 1.4% in the low exposed (GM = 0.7 ng/m^3) workers and 12.8% in the medium exposed workers(GM = 1.3 ng/m^3) to 30.4% in the high exposed workers (GM = 18.1 ng/m^3). Especially atopic workers showed a strong exposure-positive SPT relationship, whereas no clear association was found in non-atopic workers. Atopy and α-amylase exposure appeared to be the most important determinants of skin sensitisation, and atopic status was the only statistically significant determinant of positive IgE. A relationship was found between SPT to amylase and the prevalence of work-related respiratory symptoms. The prevalence of work-related respiratory rhinitis was almost five times higher in α-amylase SPT positive workers, and the prevalence of work-related chest symptoms 12 times higher.

Recently a cross-sectional study was conducted by Vanhanen et al. (130) in four bakeries, one flour mill and one crisp bread factory. Altogether 365 workers were examined and tested with the enzymes α-amylase, cellulase and xylanase. In bakeries 8% (12 of 153 tested) had a positive SPT to enzymes (12% to flours), in the flour mill 5% (3 of 62) of the subjects had SPT reactions to enzymes (5% to flours) and in the crisp bread factory 3% (4 of 150) were positive to enzymes (8% to flours). Nine out of 19 persons were sensitised to enzymes, but not to flours, and 7 of them had work-related symptoms. Four workers were sensitised only to enzymes without reactions to any other allergen tested; one of them suffered from work-related symptoms.

Two cross-sectional studies conducted in bakeries also report α-amylase sensitivities: positive SPT to α-amylase was found in 5% of British bakery and flour mill workers (30) and in 7.5% of Italian bakers (142).

Cereal flour itself contains also several enzymes. In a study on cereal amylases Sandiford et al. (117) showed that 29 out of 30 wheat flour exposed subjects with suspected hypersensitivity had positive IgE to cereal α- and β-amylases. Only 16 out of 30 had specific IgE to fungal α-amylase but whether all 30 bakers were exposed to fungal α-amylase was not mentioned. A minimal cross-reaction was observed with RAST inhibition between cereal and fungal enzymes.

Table 8a. The percentage of bakers with symptoms, positive skin prick tests and corresponding flour dust measurements. Eye and nose symptoms comprise itching of the eyes or nose, runny nose, sneezing or diagnosed rhinitis. Chest symptoms comprise tightness, wheezing, difficulty in breathing, chronic cough/phlegm or diagnosed asthma and skin symptoms eczema or itchy skin rash. Any bakery antigens include: flour, baker's yeast, mould mix, storage mites, enzymes.

Work-related symptoms (%)				Positive SPT (%)			Flour dust from personal samplers			
n	Eye and nose	Chest	Skin	Flours	Any bakery antigens	n	Range of GM mg/m^3	Range mg/m^3	Reference
183	13	9	NR	5	28	32	0.01 - 3.0	0 -4	83
96	30	17	NR	5	35	47	1.7 - 11.0	0 - 38	- " -
378	7	5	NR	NR	34	121	0.9 - 2.1*	0.2 - 12.4*	138
117	16	9	NR	NR	36	50	0.6 - 6.0*	0.1 - 113*	- " -
44	18	at least 23	5	11	NR	21	0.7 - 41.3	0.5 - 98	20
104	11	5	2	2	17	205	<1	0.1 - 16	30, 89
90	15	3	10	6	25	191	1-5	0.2 - 86	- " -
62	31	11	10	5	30	99	>5	2 - 128	- " -

*The original report gave arithmetic means see text. GMs and measuring ranges have been calculated using the original data of the report.
NR = not reported

Table 8b. The percentage of bakers with symptoms indicated as Table VIIIa, positive skin prick tests and corresponding aeroallergen measurements. Bakery antigens include: flour, baker's yeast, mould mix, storage mites, enzymes.

Work related symptoms %				Positive SPT to %		Aeroallergens from personal samplers			
n	Eye and nose	Chest	Skin	Flours	Any bakery antigens	n	Range of GM µg/m³	Range µg/m³	Reference
90	11	4	1	1	15	153	<100	8-525	30, 89
83	14	4	6	5	28	207	100-215	15-4510	-"-
83	27	10	13	6	26	159	>230	26-8320	-"-

11.1.4. Storage mites

Revsbech et al. (105) examined 23 bakery workers who suffered from nasal or pulmonary symptoms and 17 control persons with no relation to bakery work or agriculture. Among bakers specific IgE to flours was associated ($p<0.01$) with specific IgE to *A. siro* and *L. destructor* but not *T. putrescentiae*. No difference was observed between bakers and controls in positive SPT to the above-mentioned mites. However, six out of seven bakers who showed specific IgE to flours exhibited also specific IgE to storage mites. On the other hand Armentia et al. (3) reported that 12 out of 19 workers with daily occupational exposure to wheat flour had positive SPT to *L. destructor*. Five of these had specific IgE and 8 had a positive provocation test. The authors considered that the sensitisation to *L. destructor* is important in wheat flour-exposed workers who are also flour-sensitised.

In a study of British bakery workers 30% of the bakers had a positive SPT to house dust mite, *Dermatophagoides pteronyssinus*, and 77% of them had positive reactions to one or more storage mites (83). Only 14% of the bakers with a negative test to *D. pteronyssimus* showed positivity to storage mites. In the companion paper in which salt packing workers served as a control group, 33% of the bakers had a positive SPT to at least one of the storage mites, but the controls had an equal amount of positive SPT reactions. It was concluded that storage mites are not of special significance in the allergic responses of bakery workers (123). In another British study 7% of the bakers had positive SPT to *L. Destructor* (30).

De Zotti (142) reported that 18% of the examined bakers (n = 226) had a positive SPT to one or more storage mites. However, the risk of work-related symptoms was not associated with storage mite sensitisation, and it was not considered important in the occupational allergic response.

11.1.5. Fungi and insects

Hypersensitivity to the fungi *Alternaria* and *Aspergillus* has been reported in two cases of baker's asthma. In one case an inhalation challenge with *Aspergillus* mix revealed a dual asthmatic response. Precipitating *Aspergillus* antibodies were demonstrated. The second case showed an immediate type response to *Alternaria* in intradermal and bronchial challenge tests. Several fungi were cultivated from the air and the flour from the respective bakeries (64).

Specific IgE to proteins from flour beetle (*Tribolium confusum*) was observed in 9 out of 125 (7%) flour-exposed workers, suggesting that flour beetle proteins might act as occupational allergens (119). Eleven per cent of British bakers were found to be positive to *Tribolium confusum* (83).

Among 66 Danish bakers with a positive SPT to a granary weevil (*Sitophilus granarius*) extract 54% were shown to have IgE to granary weevil proteins by the RAST method, but clear evidence whether sensitisation were of occupational origin could not be provided (51).

11.1.6. Non-cereal flours

Soybean lecithin is a common additive in bakeries where it is used to improve the making and storage of bread. Wüthrich and Baur (140) reported that soybean flour components, especially lecithin can be common sensitiser among bakers. Sixty-five per cent of the bakers with occupational asthma had positive skin scratch test reaction to soya bean lecithin and 39% of bakers had lecithin specific IgE shown by RAST. Recently baker's asthma related to soybean lecithin has been reported in two bakery workers both with positive SPT, specific IgE and bronchial provocation tests to soybean components (67).

Buckwheat flour is a known occupational inhalation risk but it is rarely used in bakeries and mills compared to cereal flours. Valdivieso et al. (129) reported on a crepes-preparing baker who developed occupational asthma and contact urticaria from buckwheat flour exposure. The specificity of the allergic reactions was shown with positive bronchial provocation (both immediate and late responses), specific IgE and positive SPT to buckwheat flour extract.

An atopic noodle maker with buckwheat flour-induced asthma was described recently with positive bronchial provocation test with buckwheat and wheat flour. Specific IgE antibodies to buckwheat flour was showed with enzyme-immunoassay and immunoblotting (95).

11.1.7. Other substances occurring with flour dust

Baker's yeast have seldom been the reason for hypersensitivity disorders in bakery workers. Recently, baker's asthma caused by powered form of baker's yeast was reported. Bronchial provocation with *Saccharomyces cerevisiae* extract caused 38% decrease in FEV_1 and PEFR (peak expiratory flow rate)-monitoring during workdays showed over 25% decrease from baseline values, however when patient used conventional wet yeast PEFR values did not decrease significantly. Positive SPT reactions were found with both wet and dehydrated yeast extracts and also specific IgE to *S. cerevisiae* was measured. Bronchial provocation with baking additive extract elicited no reaction; neither did SPT with storage mites, moulds, pollens, flours or α-amylase. None of the controls had positive SPT to baker's yeast extract (13).

The development of asthma-like symptoms in 8 of 13 confectioners from the use of egg spray has been described. Skin prick test to egg extract was positive in two cases and specific IgE to ovalbumin was found in 4 confectioners (33). In addition, Blanco et al. (16) published the cases of a confectioner who used eggs to spray cakes before baking and became allergic to egg white. This was confirmed with a positive bronchial provocation test to egg white extract, and a positive skin prick test and specific IgE measurement.

The relevance of sugar dust as an occupational hazard to dental health was studied in 298 employees preparing sweets, biscuits and bakery products. The findings did not support the hypothesis that airborne sugar is an occupational dental hazard (74, 75).

Two cases of baker's asthma, rhinitis and urticaria due to sesame seed have been reported and verified by considerably decrease in PEF values when handling sesame seeds, positive SPT to sesame seed extract and specific IgE antibodies (1, 63).

Allergic respiratory symptoms from spice dust are described only occasionally and the reports are from spice mills or foodstuffs industry where spices are handled in greater amounts (91).

11.2 Effects on skin

Bakers belong to the high risk occupations for irritant contact dermatitis (111). The handling of moist doughs, frequent hand washing, and exposure to detergents cause irritant contact dermatitis; flours, flour additives and spices may also act as irritants. In addition, occupational allergic contact dermatitis and protein contact dermatitis to flours, enzymes and mites occurs, although they are rare compared to the number of exposed workers (106).

11.2.1. Flour

Pigatto et al. (100), examined 6 bakers with atopic contact dermatitis who had been exposed to flour for 1 to 20 years. All bakers had flour-specific IgE antibodies but no specific IgE to dust mite or grasses. In addition two of them were flour patch test positive, and acute dermatitis was also shown in a histological picture. Several IgE-positive dermal and epidermal cells were detected. Another four patients displayed negative or weakly positive patch test reactions to flours, and their histology bears resemblance to irritant dermatitis. All the bakers showed positive reactions in the use test with moistened flour. The control group of 10 atopic subjects had no positive test reactions at all.

In the group of 1,346 suspected contact dermatitis patients from Canadian dermatological clinics, 10 bakers were found to have occupational contact dermatitis. The working years before the onset of symptoms varied between 0.5-32 years. Seven of the bakers were diagnosed to have irritant contact dermatitis. Two bakers had a diagnosis of atopic contact dermatitis associated with the use of flours and the other had also occupational asthma related to rye flour. In addition positive patch test reactions to fragrances and spices were found in both bakers. One baker had a patch test response to fragrance mix which was believed to be related to past contactant exposure (84).

11.2.2. Enzymes and Baker's yeast

α-Amylase is a cause of protein contact dermatitis in bakers. Morren et al. (82) examined 32 bakers who had hand dermatitis: seven had positive reaction in scratch-chamber test to α-amylase (no controls were reported); five of them (5/7) had specific IgE to α-amylase and two (2/7) had also a delayed scratch-chamber test reaction to α-amylase after two days. Six of the patients had also simultaneous positive scratch chamber test reactions to flours. All seven scratch chamber

α-amylase-positive bakers had eczema on the hands and in four of them the eczema was more extensive, affecting also forearms and face. Four of the bakers experienced flare of urticaria-like lesions after a short exposure time and three of them complained of respiratory symptoms at work. Specificity of α-amylase reactions were investigated further with α-amylase SPT. All four tested bakers had positive SPT reactions to α-amylase with 1:25 mg/ml or with more dilute dilution, whereas only one of the 60 controls (a healthy volunteer) had the reaction to the dilution of 1:25 mg/ml.

Among atopic dermatitis patients with positive SPT to *Saccharomyces cerevisiae* were also two patients whose baker's yeast associated symptoms were thought to be caused by baking. The other had also SPT positivity to barley and wheat extracts. Immunoblotting with pooled sera from persons with *Saccharomyces cerevisiae* specific IgE recognised 15 allergens in baker's yeast extract (65).

11.2.3. Spices

The spices and flavourings used in bakeries are known to contain both allergens and irritants, the same compounds which are found also in fragrances.

While investigating contact sensitisation to fragrance materials Malten (72) reported that contacts with occupational flavourings were related to bakers' eczematous complaints. Four (4/7) bakers had positive patch test reactions to several fragrances, most often to cinnamic compounds. From the work substances tested only cinnamon powder caused positive patch test results in two of the bakers. One baker had strong reactions to a spice mixture, and weaker reactions to flour and yeast. The eczematous complaints of the fourth patient had not an occupational origin but difficulties were encountered when he functioned as a baker or as a cook.

In addition to cinnamon powder, which is the main bakers' spice allergen, cardamom has caused allergic hand dermatitis in a confectioner; this was confirmed with positive patch-tests to cardamom powder and oil (79).

A Swedish study of 70 spice factory workers showed that exposure also to the spices used in bakeries and confectioners may cause skin irritation, and in some cases contact allergy. Especially cinnamon powder produced both irritant and allergic reactions (76).

11.2.4. Chemicals

Contact dermatitis in bakers has been reported due to the emulsifying agent Foodmuls E3137 in the dough improver (135), the flour bleaching agent benzoyl peroxide (36) and chromium compounds in the flour (47).

12. Dose-Effect and Dose-Response Relationships

12.1. Single/short-term exposure

There are no data available on the effects of single or short-term exposure. A prerequisite for sensitisation is repeated exposure; thus, single exposure is not relevant in terms of sensitisation. The literature also lacks information on the importance of single or repeated short-term peak exposures in the process of sensitisation.

12.2. Long-term exposure

Although there is a multitude of studies on the prevalence of sensitisation and allergies among flour dust exposed bakers, surprisingly few have assessed exposure-effect relationships; full exposure-response curves are normally not computable. Only of couple of incidence studies are available (24, 52). During the past few years some studies have included data on symptoms, disease, and sensitisation in relation to the measured exposure concentrations. Some data on four of these studies have been compiled in Table 8. These studies will be described briefly.

Musk and co-workers (83) reported on 279 bakery employees. A ranking system of perceived dustiness correlated well with 79 measurements of air concentrations using personal samplers for inhalable dust. The geometric means exceeded 3 mg/m^3 only in the confectionery bakery (11 mg/m^3) and in scone production (6.6 mg/m^3). However, concentrations above 10 mg/m^3 were recorded occasionally in several bakery tasks (Table 4a). In the bakery group 35% reported some chest symptoms, 13% of whom considered them work-related. The corresponding figures for nasal symptoms were 38% and 19%. Non-specific bronchial responsiveness (PD_{20} of 30 µmol or less) was associated with a higher exposure. Positive skin tests to one or more of the bakery antigens (mixed flour, wheat flour, mould mix, baker's yeast) were found in 9% of the subjects. Thirty-three per cent had positive skin tests to storage mites. In Table 8a work-related symptoms and positive skin tests have been divided into two exposure categories according to the original paper.

Respiratory symptoms and non-specific airway responsiveness to methacholine was studied in 44 flour-exposed male workers (20). The 164 controls comprised of workers who had never been at occupational risk of exposure to wheat flour dust; they may have been exposed to other dusts in salt-packing (n = 40), stationary work (n = 27), food distribution (n = 27), glass shop (n = 55) and electrical engineering (n = 6). Total dust concentrations were measured using Millipore closed-face filter holders as personal samplers with a portable pump. The bakery was divided into five areas according to work assignment and 2-6 samples were taken at each area during 4 h periods. The flour dust concentrations are given in Table 4a. Only one area exceeded an average concentration of 3.5 mg/m^3. The

area for "special bread baking" reached an average of 41.3 mg/m^3. Looking at the situation symptomwise, there were no statistically significant differences between the flour-exposed workers and the controls (chronic bronchitis, chronic cough, phlegm, asthma, dyspnoea, runny nose, eczema, urticaria). However, "one or more symptoms" were mentioned significantly more often among the bakers than among the controls. Airway responsiveness (positive methacholine airway challenge test, MAC) was strongly associated with being flour dust exposed; the dose-response curve in the MAC-test was also steeper in flour-exposed workers than in controls. A positive skin-prick test to cereal flour antigen was found in 11% of flour-exposed and in 6% of the controls.

In the Copenhagen area 56 traditional bakeries and 9 bread factories were subjected to hygienic assessment. The objective was the prevention of allergies among bakers (98, 138). Personal air sampling of total dust (cellulose acetate filter with portable pump) on maximally 4 workers per bakery and 16 per factory was performed. The sampling time was four hours. Stationary total dust sampling at fixed sites was undertaken simultaneously. In traditional bakeries, the average flour concentrations in air varied from 1.1 to 2.9 mg/m^3 (AM) as assessed with personal samplers. In the nine factories the corresponding range of average concentrations was 1.0-14.3 mg/m^3 (AM) (Table 4a). The study included a health survey on 378 bakers representing 66.3% of the invited bakers from 99 traditional bakeries, and 117 bakers and 81 packers (as controls) from nine bread factories. The response rate was 71.2%. As a second group of controls, 150 persons of the Glostrup community were invited. The rather low response rate of 45.3% may indicate some degree of self-selection. The clinical investigations included spirometry and a bronchial inhalation test with methacholine. Prick tests with 10 environmental allergen extracts and 18 bakery allergens were performed. Peak flow recordings over a 2-week period were obtained. The diagnosis of occupational asthma was based on: i) an ascertained asthma diagnosis, ii) one or more positive skin tests with bakery allergens and iii) work-relatedness of the symptoms. Occupational rhinitis was considered proven when: a) two out of three typical symptoms were present (sneezing, nasal discharge, stuffiness of nose), b) one or more skin tests with bakery allergens were positive; and, c) there was a subjective work-relatedness of the symptoms.

Non-specific bronchial hyperresponsiveness was found in 14% of the factory workers, 8.4% in traditional bakery workers and 5% in packers. In the bread factory workers, occupational asthma was found in 8.6% and occupational rhinitis in 16.2%, respectively. The corresponding values for traditional bakery workers were 4.7% and 7.4%, respectively. Of the packers 1.2% had baker's rhinitis and none had flour asthma. These prevalences have been related to the exposure levels in Table 8a.

Recently a report relating sensitisation and allergic symptoms among bakers and mill workers to exposure to flour dusts and aeroallergens was published (30). It represents the initial cross-sectional phase of a longitudinal on-going study. It involves three modern bakeries, a flour packing factory and three mills where

wheat was milled and packed. Out of 401 eligible workers 344 participated (86%). The symptoms of 322 persons were assessed by self-administered questionnaires. The symptoms were considered work-related if they improved over the weekends or holidays, or if they were provoked by contact with flour. New symptoms were defined as symptoms reported to have started after first employment at the site. Sensitisation was assessed by skin prick tests in 335 subjects. Personal samplers were used for the air measurements and both total dust and aeroallergen concentrations were analysed. The inclusion of the measurement of aeroallergens parallel with the measurement of total dust is a comparatively new approach that may have future importance in the setting of hygienic limits on the basis of sensitising properties.

Work-related chest symptoms were reported by 14% of all participants, 29% reported eye/nose symptoms, and 9% skin symptoms. A positive skin test with flour allergens was found in 5% and with α-amylase in 5%. The work-related symptoms have been related to the exposure categories in Table 8a and b.

13. Previous Evaluations by (Inter)National bodies

The health effects of flour dust (wheat and rye flours) and α-amylase have been evaluated and these substances have been added as sensitisers to the Deutsch MAK- und BAT-Werte-Liste in 1995 (31), no specific values have been presented.

In the HSE list EH40/95 Occupational Exposure Limits 1995, flour dust is mentioned as one of the substances under the reviewing process.

The EU Scientific Group on Occupational Exposure Limits have in 1996 adopted a position paper on sensitisers which states that exposure-response data available ought be taken into consideration in the setting of LOAELs (Lowest Observable Adverse Effect Level) in order to protect a majority of workers from respiratory allergies.

14. Evaluation of Human Health Risks

14.1. Groups at extra risk

There are two identified principal factors, apart from exposure conditions, that may increase the risk of contracting occupational asthma; atopy and smoking. It is common practice to look into these parameters in epidemiological studies on occupational sensitisation.

The outcome of studies on atopy and risk of becoming sensitised to occupational agents may depend on the criteria of atopy used. The most widely used definition refers to the capacity to readily produce IgE antibodies on contact with common environmental allergens (97). Sometimes atopy is used to denote atopic

history of the studied individuals, family history of atopy or combinations of the alternatives. These definitions are known to describe populations that are far from identical (120).

Järvinen and collaborators (59) demonstrated high prevalences of asthma (9%), rhinitis (23%) and eczema (5%) among 234 bakers. According to history, skin or RAST tests, flour dust was implicated as the cause of asthma in 14 (6%) workers. Seventeen (29%) of the 58 bakers with an atopic disease had had an allergic manifestation before entering the bakery industry. The workers were not skin tested to assess atopy; atopy was determined by personal and family history. The authors construed their results as evidence of unsuitability of workers with previous or present atopic diseases for bakery work. The study is comparatively frequently quoted. It appears reasonable to assume that workers suffering from rhinitis or asthma when entering any work associated with exposure to dust will experience an aggravation of their symptoms; the higher concentrations of flour dust the more will symptoms increase. This applies probably even stronger to intrinsic asthma and vasomotoric and other non-allergic rhinitis and is not dependent on atopy. The unsuitability of non-symptomatic atopics with a history of allergy is less clear-cut.

Considering the alleged unsuitability of atopics for bakery work one ought to bear in mind a recent report showing that although 23% of bakery workers reported work-related rhinitis and/or chest tightness, IgE-mediation could be demonstrated in only one third of them, and the mechanism of the two thirds of the symptomatic bakers remained unclear (56). The non-specific, irritative effects of flour dust have lately been emphasised by other authors as well (30, 121).

Atopy is in general associated with an increased risk of becoming sensitised to high-molecular weight agents such as animal dander (28, 120) and enzymes (21). The association between sensitisation to flour allergens and atopy as demonstrated using skin tests with common environmental allergens has also been corroborated in several studies (30, 102, 142). In a bakery involving 279 studied workers, the odds ratio for atopics compared with non-atopics to have one or more positive skin test to bakery antigens was as high as 16.3 (83). Houba and co-workers reported a clear exposure-sensitization-relationship of both wheat and α-amylase allergens in 393 bakery workers. Atopy (defined as elevated total IgE or presence of specific IgE to common allergens) appeared to be an important effect modifier of this relationship (56). However, a recent report comprising 344 bakery workers found only a weak association between symptoms and specific skin sensitisation to flour. Eye, nose and skin symptoms were independent on the atopic status (30).

It is obvious that atopy increases the probability of becoming sensitised to flour. There is, however, not a strong correlation between symptoms and positive skin tests to flour allergens, and atopy and symptoms. This implies that symptoms have a non-allergic background and that non-atopics develop specific allergic diseases from flour dust exposure. Considering that atopy is a characteristic of about one third of the working population it is generally agreed that atopy, owing to its low predictive value, should not be used for pre-employment screening. Prevention

should primarily focus on the control of exposure in the occupational environment (85, 86, 92, 132).

Smoking has been claimed to increase the risk of contracting occupational asthma in some working environments. In a coffee roastery, smokers were shown to have higher IgE-levels and an increased risk of becoming specifically sensitised (93). Venables and co-workers reported that atopy was associated with sensitisation against tetrachlorophthalic anhydride; however, smoking was more strongly associated with the development of specific IgE-antibodies than atopy (134). The effect of smoking on sensitisation has also been shown in other environments but it is not a consistent finding in occupations associated with sensitisers. So far one study has revealed an association between smoking and sensitisation to bakery allergens (flour and storage mites) (142).

14.2 Assessment of health risks

Exposure to flour dusts is associated with well recognised health hazards. Any health risk assessment of the work environments associated with flour dust exposure need to consider the multitude of sensitising agents apart from flours that invariably are present. These allergens include enzymes, other flour additives, spices, and storage mites.

The prevalence of asthma and respiratory symptoms among flour exposed workers is high. In prevalence studies symptoms from the eyes and nose are frequently over 20%, symptoms from the chest range from about 5 to 20% and asthma from 5 to 11%. Moreover, studies are concerned with so-called survival populations, and almost certainly underestimates the risk. In fact, results by Prichard and co-workers (102) indicate that atopics tend to leave bakeries; the frequency of positive skin tests to environmental allergens declined with increasing duration of baking, whereas the frequency of positive skin tests with wheat increased.

Exposure conditions have not undergone the favourable change that was expected when modern and technically developed bread factories became common. Exposure levels in modern factories are as high as in traditional bakeries. Consequently, the prevalence of sensitisation, symptoms and flour dust-induced allergies has not declined (138). Dust control in traditional bakeries has likewise failed. The lack of improvements in controlling dust exposure is difficult to understand, as the technical means for reducing dust levels in bakeries are available (49). Flour concentrations during dough preparation, bread forming, and mixing of flour still display levels far above all recommendations. Peak exposures of short duration are frequent in most bakeries.

Flour-induced asthma and rhinitis have repeatedly and convincingly been shown to be IgE-mediated (15, 17, 18). However, far from all respiratory symptoms are due to specific sensitisation; non-allergic mechanisms and irritative effects ought to be born in mind (30, 121).

Specific sensitisation as demonstrated in skin tests with flour extracts among exposed populations has a range of 1-15%. However, when extracts of other flour

dust components such as enzymes, storage mites and baking yeast have been used in testing, the prevalence of positive results is frequently above 30% (Table 8). Sensitisation *per se* is not an illness. Its clinical significance and especially the predictive value of sensitisation with respect to the development of disease remains to be assessed. Positive skin tests are found in a greater proportion than IgE-mediated allergy. The rather weak association between positive skin tests with flours and symptoms (30) can be explained by the fact that other agents such as enzymes and storage mites or non-immunologic mechanisms are causing part of the symptoms.

The prevalence of respiratory symptoms is clearly dependent on exposure intensity, whereas the prevalence of sensitisation at the concentrations studied does not exhibit a similarly strong exposure-response relationships (Table 8). The importance of peak exposures in terms of sensitisation cannot be evaluated on the basis of existing data. Also non-specific bronchial hyperreactivity correlates with exposure intensity. The most detrimental outcome of sensitisation is bronchial asthma. As a rule specifically induced asthma forces the worker to change work, or at least work site. Allergic rhinitis may precede the onset of asthma and therefore calls for vigilance by the health personnel.

Atopy increases the risk of sensitisation to flour allergens. The sensitivity, specificity and predictive value of atopy, regardless of how it is defined, are low with respect to development of allergic disease, and the prevalence of atopy among working populations is high. Therefore, atopy is unsuitable for the identification of susceptible individuals; prevention by controlling exposure should be focused on.

14.3 Scientific basis for an occupational exposure limit

Symptoms from the respiratory tract and the eyes are the health effects to be prevented by setting an OEL (occupational exposure limit). Asthma is particularly important to prevent. Rhinitis precedes often the onset of asthma and is therefore likewise important. Sensitisation, i.e. the development of specific IgE-type antibodies, is not a disease. Positive skin tests with flour extracts correlate weakly with symptoms and the predictive value of sensitisation with respect to the development of disease is still unclear. The correlation between sensitisation and exposure intensity is weaker than that of symptoms and exposure intensity. Probably less than half of the symptoms are IgE-mediated. Based on current knowledge it appears both unrealistic and not sufficiently founded to suggest an OEL to prevent sensitisation; however, sensitised individuals should be subjected to careful supervision by health personnel.

Existing data on exposure-response relationships do not allow the identification of a NOAEL (No Observable Adverse Effect Level) for flour dust. Due to the nature of allergy it is unlikely that the setting of a NOAEL for flour dust will be practicable even in the future. The setting of an LOAEL should aim at the protection of a vast majority of the exposed; however, such an LOAEL will not necessarily protect already sensitised individuals from elicitation of symptoms by the inducing flour.

A flour dust level of above 5 mg/m^3 is associated with a prevalence of work-related chest symptoms of some 9-17% and work-related rhinitis/conjunctivitis of 16-31% (30, 83, 138). The corresponding values at geometrical mean below 5 mg/m^3 are for chest symptoms 3-9% and for rhinitis/conjunctivitis (7-15%). Wilhardt et al., (138) reported 5% of work-related asthma and 7% of rhinitis at geometrical means (calculated using the original data of the paper) of 0.9-2.1 mg/m^3 for flour dust. Current data indicate that existing occupational exposure limits for flour dust (total/organic dust) which are in the range of 3-15 mg/m^3 will allow high prevalences of sensitisation, symptoms and allergic diseases as well as disorders caused by non-immunological mechanisms. A factor of uncertainty remains as the importance of peak exposures is unknown.

Peak exposures reaching high concentrations are frequent and may last up to 30 minutes in some operations. The setting of a STEL (short term exposure limit) appear necessary to control such exposures. It is difficult to derive a STEL from current scientific data.

15. Research needs

There is much information on exposure levels to flour at various sites in bakeries, prevalences of sensitisation to flour products, and symptoms and diseases. However, few studies have combined exposure measurements and detrimental outcomes of the exposure in a way that would provide valuable exposure-response data for the establishment of health-based OELs. This is especially true for low exposure levels. The recording of symptoms and diseases as well as the levels of flour dust have not been conducted in a consistent manner and hence hinders comparisons between studies.

Prevalences of allergic symptoms are frequently given without a careful assessment of the immunological background. This pertains especially to symptoms observed for the eyes and upper respiratory tract. When setting an OEL it is of importance to understand the nature of the disease; for instance, non-specific irritative symptoms cannot be compared with asthma due to specific sensitisation with respect to severeness. However, a great many of respiratory symptoms are not due to specific sensitisation; therefore, non-allergic mechanisms and irritative effects should be examined in bakers' with respiratory symptoms.

Prevalence studies should be supplemented by retrospective studies of workers who have left there work to assess the degree of leaving due to symptoms and diseases. Sensitisation is a result of an immunological reaction and is not as such a disease. Sensitisation is constantly reported more frequently than allergic diseases. Thererfore, the prognostic importance of sensitisation should be assessed by longitudinall studies. This type of study has rarely been attempted although there is at least one study presently being conducted (30). Such studies are expensive and are vulnerable to a high degree of drop out. However, the studies still generate useful

information because prevalence studies of allergic manifestations such as asthma always suffer from several biases pertaining to both active and unconscious selection in addition to the so-called "healthy worker effect". Longitudinal studies also assess the importance of individual susceptibility linked to, e.g. atopy and smoking in a more reliable way than cross-sectional studies.

The use of standardised methods with size-selective sampling devices for flour dust measurements should be emphasised to obtain more accurate and comparable flour dust concentration results from different studies in the future. It has also been suggested that short term peak exposures are more important in the development of asthma and other allergies than low exposure over a long period of time (71, 133). The importance of peak exposures in bakeries has not been studied. Peak exposures appear to be frequent in bakeries. Thus they contribute importantly to the full shift TWA exposure. Although this issue is crucial it may be difficult to solve as effects induced by peak exposures and daily averages are hard to separate from each other.

Some studies have used various immunological methods to assess the levels of aeroallergens in the air and also in relation to sensitisation and symptoms. This approach may prove important for the establishment of exposure limit values in the future. However, there are so far differences between various assays yielding different results. The development of standardised assays and continuous interlaboratory comparisons appear imperative before aeroallergen levels can be used to establish limit values.

Due to the nature of allergy it appears unrealistic in the near future to achieve a 100% protection of workers from sensitisation and, especially to protect already sensitised symptomatic individuals by setting OELs. However, it is obviously possible to reduce both the rate of sensitisation and the incidence of symptoms and respiratory diseases by reducing exposure levels. The immediate objective should be to protect a majority of workers by using existing data in the setting of OELs. Technically the control of exposure should not be too difficult, especially not in large factories, whereas small bakeries (less than 10 persons) need simple and cheap solutions. Intervention studies in bakeries where the exposure is being controlled will be needed to evaluate the efficiency of the LOAEL for flour dust.

16. Summary

Tiikkainen U, Louhelainen K, Nordman H. Flour Dust. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. *Arbete och Hälsa* 1996;27.

High flour exposure levels are common and short-time peak exposures are frequent in bakeries. The critical health effects are symptoms from the respiratory tract and the eyes, allergic rhinitis and asthma. IgE-mediation can be confirmed only in less than 50% of symptomatic workers implying that non-immunologic mechanisms are also involved. Specific sensitisation is more frequent than allergic disease; however, the prognostic importance of sensitisation is unknown. The prevalence of symptoms, allergic rhinitis and asthma are high at all currently used hygienic limits (range 3-15 mg/m^3). When considering preventive measures it is necessary to consider other agents including enzymes and spices which may cause similar health effects as flours.

Keywords: allergy, exposure levels, occupational exposure limits, flours, bakery allergens, health effects, risk assessment, sensitisation, review

17. Summary in Swedish

Tiikkainen U, Louhelainen K, Nordman H. Flour Dust. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. *Arbete och Hälsa* 1996;27.

Exponering för höga halter mjöldamm är vanligt och korttidsexponering förekommer ofta i bagerier. De kritiska effekterna bedöms vara symptomen från luftvägar och ögon, allergisk rinit och astma. Vissa symptom och sjukdomar orsakas av sensibilisering till mjöl. IgE-mediering kan dock faställas hos mindre än 50% av arbetare med symptom. Det prognostiska värdet av sensibilisering är dock oklart. Specifik sensibilisering är mera frekvent än allergiska sjukdomar. Prevalens av allergisk rinit och astma är högt vid alla nuvarande hygieniska gränsvärden (3-15 mg/m^3). I samband med preventiva åtgärder är det nödvändigt att ta hänsyn till andra agens såsom enzymer, kryddor och kvalster som kan orsaka likadana effekter som mjöl.

Nyckelord: Allergi, exponerings nivå, hygieniska gränsvärden, mjöl, bagare allergen, hälsoeffekter, riskuppskattning, sensibilisering, översikt

18. References

1. Alday E, Curiel G, Lopezgil MJ, Carreno D, Moneo I. Occupational hypersensitivity to sesame seeds. *Allergy* 1996;51:69-70.
2. Armentia A, Sanchez-Monge R, Gomez L, Barber D, Salcedo G. In vivo allergenic activities of eleven purified members of a major allergen family from wheat and barley flour. *Clin Exp Allergy* 1993;23:410-415.
3. Armentia A, Tapias J, Barber D, et al. Sensitization to the storage mite Lepidoglyphus destructor in wheat flour respiratory allergy. *Ann Allergy* 1992;68:398-403.
4. Awad El Karim MA, Gad El Rab MO, Omer AA, El Haimi YAA. Respiratory and allergic disorders in workers exposed to grain and flour dusts. *Arch Environ Health* 1986;41:297-301.
5. Bachmann M, Myers JE. Grain dust and respiratory health in South African milling workers. *Br J Ind Med* 1991;48:656-662.
6. Baldo BA, Baker RS. Inhalant allergies to fungi:reactions to bakers' yeast (Saccharomyces cerevisiae) and indentification of bakers' yeast enolase as an important allergen. *Int Arch Allergy Appl Immunol* 1988;86:201-208.
7. Baldo BA, Krilis S, Wrigley CW. Hypersensitivity to inhaled flour allergens. Comparison between cereals. *Allergy* 1980;35:45-56.
8. Baldo BA, Wrigley CW. IgE antibodies to wheat flour components. *Clin All* 1978;8:109-124.
9. Barber D, Pernas M, Chamorro MJ, et al. Specific depletion of the house dust mite allergen Der p 1 by cereal flour prolamins. *J Allergy Clin Immunol* 1996;97:963-965.
10. Barber D, Sanchez-Monge R, Gomez L, et al. A barley flour inhibitor of insect alpha-amylase is a major allergen associated with baker's asthma disease. *FEBS Lett* 1989;248:119-122.
11. Baur X, Chen Z, Sander I. Isolation and denomination of an important allergen in baking additives: alpha-amylase from Aspergillus oryzae (Asp o II). *Clin Exp Allergy* 1994;24:465-470.
12. Baur X, Fruhmann G, Haug B, Rasche B, Reiher W, Weiss W. Role of aspergillus amylase in baker's asthma. *Lancet* 1986;1:43.
13. Belchi-Hernandez J, Mora-Gonzalez A, Iniesta-Perez J. Baker's asthma caused by Saccharomyces cerevisiae in dry powder form. *J Allergy Clin Immunol* 1996;97:131-134.
14. Beritic-Stahuljak D, Valic F, Cigula M, Butkovic D. Simultaneous exposure to airborne flour particles and thermal load as a cause of respiratory impairment. *Int Arch Occ Env Health* 1976;37:193-203.
15. Björkstén F, Backman A, Järvinen KAJ, Lehti H, Savilahti E, Syvänen P, Kärkkäinen T. Immunoglobulin E specific to wheat and rye flour proteins. *Clin All* 1977;7:473-483.
16. Blanco Carmona JG, Juste Picón S, Garcés Sotillos M, Rodriques Gastón P. Occupational asthma in the confectionary industry caused by sensitivity to egg. *Allergy* 1992;47:190-191.
17. Blands J, Kallós P, Kallós-Deffner L, Lowenstein H. Flour allergy in bakers. I Identification of allergenic fractions in flour and comparision of diagnostic methods. *Int Arch Allergy Appl Immunol* 1976;52:392-406.
18. Block G, Tse KS, Kijek K, Chan H, Chan-Yeung M. Baker's asthma. Clinical and immunological studies. *Clin Allergy* 1983;13:359-370.
19. Block G, Tse KS, Kijek K, Chan H, Chan-Yeung M. Baker's asthma. Studies of the cross-antigenicity between different cereal grains. *Clin All* 1984;14:177-185.
20. Bohadana AB, Massin N, Wild P, Kolopp M-N, Toamain J-P. Respiratory symptoms and airway responsiveness in apparently healthy workers exposed to flour dust. *Eur Respir J* 1994;7:1070-1076.
21. Brisman J. Industrial enzymes. *Arbete och Hälsa* 1994;28.

22. Brisman J, Belin L. Clinical and immunological responses to occupational exposure to alpha-amylase in the baking industry. *Br J Ind Med* 1991;48:604-608.
23. Brisman J, Lillienberg L, Järvholm B. Exposure to flour dust and respiratory disease in bakers. In: *25th International Congress on Occupational Health, Book of Abstracts II.* Stockholm 15-20 September 1996:117 (Abstract).
24. Brisman SJ, Järvholm BG. Occurrence of self-reported asthma among Swedish bakers. *Scand J Work Environ Health* 1995;21:487-493.
25. Brown MA. Nioh and niosh basis for an occupational health standard:Grain dust. Health hazards of storing, handling and shipping grain. *Arbete och Hälsa* 1988;14:63.
26. Burdorf A, Lillienberg L, Brisman J. Characterization of exposure to inhalable flour dust in Swedish bakeries. *Ann Occup Hyg* 1994;38:67-78.
27. Bush RK, Schroeckenstein D, Meier-Davis S, Balmes J, Rempel D. Soybean flour asthma: detection of allergens by immunoblotting. *J Allergy Clin Immunol* 1988;82:251-255.
28. Cockroft A, Edwards J, Mccarthy P, Andersson N. Allergy and laboratory animal workers. *Lancet* 1981;2:827-830.
29. Cowherd C Jr, Grenlinger MA, Englehart PJ, Kent RF, Wong KF. An apparatus and methodology for predicting the dustiness of materials. *Am Ind Hyg Assoc J* 1989;3:123-130.
30. Cullinan P, Lowson D, Nieuwenhuijsen MJ, et al. Work related symptoms, sensitisation, and estimated exposure in workers not previously exposed to flour. *Occup Environ Med* 1994;51:579-583.
31. Deutsche Forschungsgemeinschaft. *MAK- und BAT-Werte-Liste 1995. Maximale Arbeitsplatzkonzentrationen und Biologische Abeitsstofftoleranzwerte.* 31st ed., 1995.
32. Van Dishoeck HAE, Roux DJ. Sensitization to flour and flour illnesses amongst flour workers. *Journal of Hygiene* 1939;39:674-679.
33. Edwards JH, McConnochie K, Trotman DM, Collins G, Saunders MJ, Latham SM. Allergy to inhaled egg material. *Clin All* 1983;13:427-432.
34. European Committee for Standardisation. Workplace atmospheres - Size fraction definitions for measurement of airborne particles. In: *European Standard EN 481.* 1993.
35. Fakhri ZI. Causes of hypersensitivity reactions in flour mill workers in Sudan. *Occup Med* 1992;42:149-154.
36. Fisher A. Allergic bakers' dermatitis due to benzoyl peroxide. *Cutis* 1989;43:128-129.
37. Fonn S, Groeneveld HT, De Beer M, Becklake MR. An environmental and respiratory health survey of workers in a grain mill in the Johannesburg area, South Africa. *Am J Ind Med* 1993;24:387-400.
38. Fonn S, Groeneveld HT, De Beer M, Becklake MR. Relationship of respiratory health status to grain dust in a Witwatersrand grain mill: Comparison of workers' exposure assessment with industrial hygiene survey findings. *Am J Ind Med* 1993;24:401-411.
39. Fränken J, Stephan U, Meyer HE, König W. Identification of alpha-amylase inhibitor as a major allergen of wheat flour. *Int Arch Allergy Immunol* 1994;104:171-174.
40. Fränken J, Stephan U, Neuber K, Bujanowski-Weber J, Ulmer WT, König W. Characterization of allergenic components of rye and wheat flour (Secale, Triticum vulgaris) by western blot with sera of bakers: their effects on CD23 expression. *Int Arch Allergy Appl Immunol* 1991;96:76-83.
41. Gadborg E. *Om Melallergi* (Thesis). Københavns Universitet, 1956. 83 p.
42. García-Casado G, Armentia A, Sánchez-Monge R, Malpica JM, Salcedo G. Rye flour allergens associated with baker's asthma. Correlation between in vivo and in vitro activities and comparison with their wheat and barley homologues. *Clin Exp Allergy* 1996;26:428-435.
43. Gimenez C, Fouad K, Choudat D, Laureillad J, Bouscaillou P, Leib E. Chronic and acute resiratory effects among grain mill workers. *Int Arch Occup Environ Health* 1995;67:311-315.

44. Gómez L, Martin E, Hernández D, et al. Members of the alpha-amylase inhibitors family from wheat endosperm are major allergens associated with baker's asthma. *FEBS Lett* 1990;261:85-88.

45. Grenquist-Nordén B, Tiikainen U, Klockars M, Mutanen P, Nordman H. The development of flour specific IgG1 and IgG4 antibodies in baker apprentices. In: *25th International Congress on Occupational Health. Book of Abstracts I*. Stockholm 15-20 September 1996:201 (Abstract).

46. Van Hage Hamsten M, Johansson SG. Storage mites. *Exp Appl Acarol* 1992;16:117-128.

47. Heine A, Fox G. Bäckerekzem durch Chromverbindungen in Mehlen. *Dermatosen* 1980;28:113-115. (In German).

48. Heinonen K, Enbom S. *Pölyntorjunta Elintarviketeollisuudessa*. (Dust control in the food-production industry). Helsinki, Finland: Työsuojelurahasto, 1994. (Research report in Finnish).

49. Heinonen K, Kulmala I, Säämänen A. Local ventilation for powder handling - combination of local supply and exhaust air. *Am Ind Hyg Assoc J* 1996;57:356-364.

50. Hendrick DJ, Davies RJ, Pepys J. Bakers' asthma. *Clin All* 1976;6:241-250.

51. Herling C, Svendsen UG, Schou C. Identification of important allergenic proteins in extracts of the granary weevil (Sitophilus granarius). *Allergy* 1995;50:441-446.

52. Herxheimer H. The skin sensitivity to flour of bakers' apprentices. *Acta Allergol* 1973;28:42-49.

53. Hjorth N, Roed-Petersen J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 1976;2:28-42.

54. Holgate ST. The process of airway inflammation and its relationship to clinical symptoms. In: Johansson SGO, ed. *Progress in Allergy and Clinical Immunology. Proceedings of the XVth International Congress of Allergology and Clinical Immunology*. v. 3. Stockholm: Hogrefe & Huber Publishers, 1995:50-54.

55. Hoseney RC. Dry milling of cereals. In: Hoseney RC, ed. *Principles of Cereal Science and Technology*. St. Paul, Minnesota, USA: American Assiciation of Cereal Chemists Inc., 1986:133-152.

56. Houba R. *Occupational respiratory allergy in bakery workers*. Relationships with wheat and fungal -amylase aeroallergen exposure (Thesis). Landbouwuniversiteit Wageningen, 1996. 172 p.

57. Houba R, Heederik DJJ, Doekes G, van Run PEM. Exposure-sensitization relationship for -amylase allergens in the baking industry. *Amer J Respir Crit Care Med* 1996;154:130-136.

58. Houba R, van Run P, Heederik D, Doekes G. Wheat antigen exposure assessment for epidemiological studies in bakeries using personal dust sampling and inhibition ELISA. *Clin Exp Allergy* 1996;26:154-163.

59. Järvinen KAJ, Pirilä V, Björkstén F, Keskinen H, Lehtinen M, Stubb S. Unsuitability of bakery work for a person with atopy: a study of 234 bakery workers. *Ann Allergy* 1979;42:192-195.

60. Jauhiainen A, Louhelainen K, Linnainmaa M. Exposure to dust and alpha-amylase in bakeries. *Appl Occup Environ Hyg* 1993;8:721-725.

61. Johansson E, Johansson SGO, van Hage-Hamsten M. Allergic characterization of Acarus siro and Tyrophagus putrescentiae and their crossreactivity with Lepidoglyphus destructor and Dermatophagoides pteronyssinus. *Clin Exp Allergy* 1994;24:743-751.

62. Kasarda DD, Bernardin JE, Nimmo CC. Wheat proteins. In: Pomeranz Y, ed. *Advances in Cereal Science and Technology*. v. 1. St. Paul Minnesota: American Association of Cereal Chemists Inc., 1976:158-236.

63. Keskinen H, Östman P, Vaheri E, Tarvainen K, Grenquist-Nordén B, Karppinen O, Nordman H. A case of occupational asthma, rhinitis and urticaria due to sesame seed. *Clin Exp Allergy* 1991;21:623-624.

64. Klaustermeyer WB, Bardana EJ, Hale FC. Pulmonary hypersensitivity to Alternaria and Aspergillus in baker's asthma. *Clin All* 1977;7:227-233.

65. Kortekangas-Savolainen O, Savolainen J, Lantto R, Kalimo K. Immediate hypersensitivity to bakery, brewery and wine products in yeast-sensitive atopic dermatitis patients. *Clin Exp Allergy* 1994;24:836-842.

66. Lahti A. Immediate contact reactions. In: Rycroft RJ, Ménne T, Frosch PJ, eds. *Textbook of Contact Dermatitis*. 2nd ed. Berlin Heidelberg: Springer-Verlag, 1995:62-74.

67. Lavaud F, Perdu D, Prévost A, Vallerand H, Cossart C, Passemard F. Baker's asthma related to soybean lecithin exposure. *Allergy* 1994;49:159-162.

68. Lillienberg L, Brisman J. Flour dust in bakeries - a comparision between methods. *Ann Occup Hyg* 1994;38, supplement 1:571-575.

69. Lillienberg L, Brisman J. Peak exposure concentrations of dust in bakeries. In: *Second International Symposium on Modern Principles of Air Monitoring*. Sälen, Sweden 5-8 February 1996.

70. Louhelainen K, Eskelinen T, Terho EO, et al. *Pölyaltistus, hengitystieoireet ja lämpökuormitus elintarviketeollisuudessa*. Kuopio, Finland: Kuopion Aluetyöterveyslaitos, 1989 (Raporttisarja 3). (In Finnish).

71. Malo JL, Chan-Yeung M. Population surveys of occupational asthma. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI, eds. *Asthma in the workplace*. New York: Marcel Dekker Inc., 1993:145-170.

72. Malten KE. Four bakers showing positive patch-tests to a number of fragrance materials, which can also be used as flavors. *Acta Derm Venereol Suppl Stockh* 1979;85:117-121.

73. Mark D, Wincent WA. A new personal sampler for airborne total dust in workplaces. *Ann Occup Hyg* 1986;30:89-102.

74. Masalin KE, Degerth RK, Murtomaa HT. Airborne sugar and flour dust in the Finnish confectionary industry. *Appl Ind Hyg* 1988;3:231-235.

75. Masalin K, Murtomaa H, Meurman JH. Oral health of workers in the modern Finnish confectionery industry. *Community Dent Oral Epidemiol* 1990;18:126-130.

76. Meding B. Skin symptoms among workers in a spice factory. *Contact Dermatitis* 1993;29:202-205.

77. Mena M, Sanchez-Monge R, Gomez L, Salcedo G, Carbonero P. A major barley allergen associated with baker's asthma disease is a glycosylated monomeric inhibitor of insect alpha-amylase: cDNA cloning and chromosomal location of the gene. *Plant Mol Biol* 1992;20:451-458.

78. Meredith S, Nordman H. Occupational asthma: Measures of frequency from four countries. *Thorax* 1996;54:435-440.

79. Mobacken H, Fregert S. Allergic contact dermatitis from cardamom. *Contact Dermatitis* 1975;1:175-176.

80. Moneo I, Alday E, Gonzalez-Munoz M, Maqueda J, Curiel G, Lucena R. Alpha-amylase hypersensitivity in non-exposed millers. *Occup Med* 1994;44:91-94.

81. Moneo I, Alday E, Sanchez-Agudo L, Curiel G, Lucena R, Calatrava JM. Skin-prick tests for hypersensitivity to alpha-amylase preparations. *Occup Med* 1995;45:151-155.

82. Morren MA, Janssens V, Dooms-Gossens A, Van Hoeyveld E, Cornelis A, De Wolf-Peeters C, Heremans A. Alpha-amylase, a flour additive: an important cause of protein contact dermatitis in bakers. *J Am Acad Dermatol* 1993;29(Pt 1):723-728.

83. Musk AW, Venables KM, Crook B, et al. Respiratory symptoms, lung function and sensitisation to flour in a British bakery. *Br J Ind Med* 1989;46:636-642.

84. Nethercott JR, Holness DL. Occupational dermatitis in food handlers and bakers. *J Am Acad Dermatol* 1989;21:485-490.

85. Newill CA, Evans R, Khoury MJ. Preemployment screening for allergy to laboratory animals: Epidemiological evaluationof its pontential usefulness. *J Occup Med* 1986;28:1158-1164.

86. Newman Taylor AJ. Occupational asthma. In: Parkers RW, ed. *Occupational Lung Disorders*. third ed. Oxford: Butterworth-Heinemann Ltd, 1994:710-729.

87. Nieuwenhuijsen MJ, Lowson D, Venables KM, Taylor AJN. Correlation between different measures of exposure in a cohort of bakery workers and flour millers. *Ann Occup Hyg* 1995;39:291-298.

88. Nieuwenhuijsen MJ, Lowson D, Venables KM, Taylor AJN. Flour dust exposure variability in flour mills and bakeries. *Ann Occup Hyg* 1995;39:299-305.

89. Nieuwenhuijsen MJ, Sandiford CP, Lowson D, Tee RD, Venables KM, McDonald JC, Newman-Taylor AJ. Dust and flour aeroallergen exposure in flour mills and bakeries. *Occup Environ Med* 1994;51:584-588.

90. Nieuwenhuijsen MJ, Sandiford CP, Lowson D, Tee RD, Venables KM, Newman-Taylor AJN. Peak exposure concentrations of dust and flour aeroallergen in flour mills and bakeries. *Ann Occup Hyg* 1995;39:193-201.

91. Niinimäki A. Spice allergy. *Investications on the prevalence of the positive skin test reactions and the appearance of clinical symptoms* (Thesis). University of Oulu, Finland, 1995.

92. Nordman H. Atopy and work. *Scand J Work Environ Health* 1984;10:481-485.

93. Österman K, Zetterström O, Johansson SGO. Coffee worker's allergy. *Allergy* 1982;37:313-322.

94. Osborne TB. Classification of vegetable proteins. In: Osborne TB, ed. *Vegetable proteins*. 2nd ed. London: Longmans, Green and co., 1924:153.

95. Park HS, Nahm DH. Buckwheat flour hypersensitivity: An occupational asthma in a noodle maker. *Clin Exp Allergy* 1996;26:423-427.

96. Parkes RW. Aerosols their deposition and clearance. In: Parkers RW, ed. *Occupational Lung Disorders*. third ed. Oxford: Butterworth-Heinemann Ltd, 1994:35-49.

97. Pepys J. Immunopathology of allergic lung disease. *Clin All* 1973;2:1-22.

98. Petersen NL, Mikkelsen S, Wilhardt P. Allergenic sensitisation and allergic diseases in Danish bakers. In: *25th International Congress on Occupational Health. Book of Abstracts I.* Stockholm 15-20 September 1996:282 (Abstract).

99. Pfeil T, Schwabl U, Ulmer WT, König W. Western blot analysis of water-soluble wheat flour (Triticum vulgaris) allergens. *Int Arch Allergy Appl Immunol* 1990;91:224-231.

100. Pigatto PD, Polenghi MM, Altomare GF. Occupational Dermatitis in bakers: a clue for atopic contact dermatitis. *Contact Dermatitis* 1987;16:263-271.

101. Popp W, Zwick H, Rauscher H. Short-term sensitizing antibodies in bakers' asthma. *Int Arch Allergy Immunol* 1988;86:215-219.

102. Prichard MG, Ryan G, Musk AW. Wheat flour sensitisation and airways disease in urban bakers. *Br J Ind Med* 1984;41:450-454.

103. Quirce S, Cuevas M, Díes-Gómes ML, Fernándes-Rivas M, Hinojosa M, González R, Losada E. Respiratory allergy to Aspergillus-derived enzymes in bakers' asthma. *J Allergy Clin Immunol* 1992;90:970-978.

104. Ramazzini B. Diseases of bakers and millers. In: Wright WC, ed. *Diseases of workers - De morbis artificum*. New York, USA: Hafner Publishing Company, Inc., 1713:225-235.

105. Revsbech P, Dueholm M. Storage mite allergy among bakers. *Allergy* 1990;45:204-208.

106. Rietschel RL, Fowler JFJ. Occupational dermatitis. In: Rietschel RL, Fowler JFJ, eds. *Fischer's Contact Dermatitis*. 4th ed. Baltimore: Williams & Wilkinson, 1995:1117.

107. Rihs HP, Rozynek P, Maytaube K, Welticke B, Baur X. Polymerase chain reaction based cDNA cloning of wheat profilin: A potential plant allergen. *Int Arch Allergy Immunol* 1994;105:190-194.

108. Romagnani S. T-cells, cytokines, and IgE regulation in allergic disease. In: Johansson SGO, ed. *Progress in Allergy and Clinical Immunology. Proceedings of the XVth International Congress of Allergology and Clinical Immunology*. v. 3. Stockholm: Hogrefe & Huber Publishers, 1995:5-12.

109. Rósen G, Andersson Ing-M, Juringe L, Rask L. PIMEX. En method för arbetsmiljöförbättringar. *Arbete och Hälsa* 1992;25.

110. Rosenberg N, Rameix F, Demangeat G, Philippon JJ, Rigault MH, Schlacther T, Sandret N. Prevalence of respiratory allergy in Paris bakeries in 1987. *Arch mal prof* 1991;52:33-36.

111. Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Ménne T, Frosch PJ, eds. *Textbook of Contact Dermatitis*. 2nd ed. Berlin: Springer-Verlag, 1995:341-400.

112. Sala E, Hytönen M, Tupasela O, Estlander T. Occupational laryngitis with immediate allergic or immediate type specific chemical hypersensitivity. *Clin Otolaryngol* 1996;21:42-48.

113. Sanchez-Monge R, Gomez L, Barber D, Lopez-Otin C, Armentia A, Salcedo G. Wheat and barley allergens associated with baker's asthma. Glycosylated subunits of the alpha-amylase-inhibitor family have enhanced IgE-binding capacity. *Biochem J* 1992 Jan 15;281(Pt 2):401-405.

114. Sandiford CP, Nieuwenhuijsen MJ, Tee RD, Newman Taylor AJ. Determination of the size of airborne flour particles. *Allergy* 1994;49:891-893.

115. Sandiford CP, Nieuwenhuijsen MJ, Tee RD, Newman-Taylor AJ. Measurement of airborne proteins involved in Bakers' asthma. *Clin Exp Allergy* 1994;24:450-456.

116. Sandiford CP, Tatham A, Jones MG, Fido R, Tee RD, Shewry PR, Newman Taylor AJ. Identification of prolamin allergens involved in cereal hypersensitivity. In: *Abstracts of the 52nd Annual Meeting. American Academy of Allergy Asthma & Immunology*. New Orleans 15-20 March 1996:79 (Abstract).

117. Sandiford CP, Tee RD, Newman Taylor AJ. The role of cereal and fungal amylases in ceral flour hypersensitivity. *Clin Exp Allergy* 1994;24:549-557.

118. Sandiford CP, Tee RD, Newman-Taylor AJ. Identification of crossreacting wheat, rye, barley and soya flour allergens using sera from individuals with wheat-induced asthma. *Clin Exp Allergy* 1995;25:340-349.

119. Schultze-Werninghaus G, Zachgo W, Rotermund H, et al. Tribolium confusum (confused flour beetle, rice flour beetle)--an occupational allergen in bakers: demonstration of IgE antibodies. *Int Arch Allergy Appl Immunol* 1991;94:371-372.

120. Slovak AJM, Hill RN. Laboratory animal Allergy: A clinical survey of an exposed population. *Br J Ind Med* 1981;38:38-41.

121. Smith TA, Lumley KPS. Work-related asthma in a population exposed to grain, flour and other ingredient dusts. *Occup Med* 1996;46:37-40.

122. Susitaival P. *Epidemiological Study of Hand Dermatoses and Other Skin Diseases in a Cohort of Finnish Farmers* (Thesis). University of Kuopio, 1996.

123. Tee RD, Gordon DJ, Gordon S, et al. Immune response to flour and dust mites in a United Kingdom bakery. *Br J Ind Med* 1992;49:581-587.

124. Thiel H, Ulmer WT. Bakers' asthma:Development and possibility for treatment. *Chest* 1980;78:400-405.

125. Thomas WR. Mite allergens groups I-VIII. A catalogue of enzymes. *Clin Exp Allergy* 1993;23:350-353.

126. Tiikkainen U, Klockars M. Clinical significance of IgG subclass antibodies to wheat flour antigens in bakers. *Allergy* 1990;45:497-504.

127. Topping MD, Forster HW, Ide CW, Kennedy FM, Leach AM, Sorkin S. Respiratory allergy and specific immunoglobin E and immunoglobin G antibodies to reactive dyes used in the wool industry. *J Occup Med* 1989;31:857-862.

128. Tossavainen A, Jaakkola J. Occupational exposure to chemical agents in Finland. *Appl Occup Environ Hyg* 1994;9:28-31.

129. Valdivieso R, Moneo I, Pola J, Munoz T, Zapata C, Hinojosa M, Losada E. Occupational asthma and contact urticaria caused by buckwheat flour. *Ann Allergy* 1989;63:149-152.

130. Vanhanen M, Tuomi T, Hokkanen H, et al. Enzyme exposure and enzyme allergy in the baking industry. *Occup Environ Med* 1996;53:670-676.

131. Varjonen E, Savolainen J, Mattila L, Kalimo K. IgE-binding components of wheat, rye, barley and oats recognized by immunoblotting analysis with sera from adult atopic dermatitis patients. *Clin Exp Allergy* 1994;24:481-489.

132. Venables KM. Preventing occupational asthma. *Br J Ind Med* 1992;49:817-819.

133. Venables KM. Prevention of occupational asthma. *Eur Respir J* 1994;7:768-778.

134. Venables KM, Topping MD, Howe W, Luczynska CM, Hawkins R, Newman Taylor AJ. Interaction of smoking and atopy in producing specific IgE antibody against hapten protein conjugate. *BMJ* 1985;290:201-204.

135. Vincenzi C, Stinchi C, Ricci C, Tosti A. Contact dermatitis due to an emulsifying agent in a baker. *Contact Dermatitis* 1995;32:57.

136. Walsh BJ, Wrigley CW, Musk AW, Baldo BA. A comparison of the binding of IgE in the sera of patients with bakers' asthma to soluble and insoluble wheat-grain proteins. *J Allergy Clin Immunol* 1985;76:23-28.

137. Weiss W, Vogelmeier C, Gorg A. Electrophoretic characterization of wheat grain allergens from different cultivars involved in bakers' asthma. *Electrophoresis* 1993;14:805-816.

138. Wilhardt P, Mikkelsen S, Nüchel Petersen L, Wittrock J. *Forebyggelse af allergi hos bagare. Kortlægning af melstøvseksponering og helbredsundersøgelser*. Køpenhavn: Arbejdsmiljøfondet, 1993 (Forskningsrapport). (In Danish, English abstract).

139. Wüthrich B. Protein contact dermatitis. *Br J Dermatol* 1995;135:332-333.

140. Wüthrich B, Baur X. Baking ingredients, especially alpha-amylase, as occupational inhalation allergens in the baking industry. *Schweiz Med Wochenschr* 1990;120:446-450. (In German, English abstract).

141. Van der Zee JS, Aalberse RC. The role of IgG in immediate-type hypersensitivity. *Eur Respir J Suppl* 1991;13:91-96.

142. De Zotti R, Larese F, Bovenzi M, Negro C, Molinari S. Allergic airway disease in Italian bakers and pastry makers. *Occup Environ Med* 1994;51:548-552.

143. Zuskin E, Mustajbegovic J, Schachter EN, Kern J. Respiratory symptoms and ventilatory function in confectionery workers. *Occup Environ Med* 1994;51:435-439.

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Appendix 1

Occupational exposure limits (8-hour time-weighted averages) for organic dust in air (mg/m^3)

Country	Total dust	Inhalable dust	Respirable dust	Comments	Year	References
Denmark	3				1992	1
Finland	5				1996	2
Iceland	5				1989	3
Norway	5				1996	4
Sweden	5				1993	5
France		10	5	PNSE[1)]	1993	6
UK		10	5		1995	7
Germany			6	flour dust defined as sensitiser	1996	8
USA		10	3	PNOC[2)] / ACGIH	1995	9
	15		5	OSHA	1995	9

1) Particulates with no specific effect

2) Particulates not otherwise classified, ACGIH

References:

1. Grænseværdier for stoffer og materialer. At-anvisning Nr. 3.1.0.2 Januar 1992, Arbejdstilsynet.

2. HTP-arvot 1996.Työministeriön turvallisuustiedote Nro 25, Työministeriö.

3. Mengunarmörk og adgerdir til ad draga ur mengun. Skra yfir mengunarmörk, Reykjavik: Vinnueftirlit rikisins 1989.

4. Administrative normer for forurensning i arbeidsatmosfære 1996. Best. nr. 361, Arbeidstilsynet.

5. Hygieniska gränsvärden, AFS 1993:9, Arbetarskyddsstyrelsens författningssamling.

6. Valeurs limites d'exposition professionelle aux agents chimiques en France. Cahiers de notes documentaires 153, 4e trimestre 1993, (ND 1945-153-93).

7. Occupational exposure limits 1995. EH40/95. Health and Safety Executive 1995.

8. MAK- und BAT-Werte-Liste, 1996. Mitteilung 32. Deutsche Forschungsgemeinschaft.

9. Guide to occupational exposure values-1995. American Conference of Governmental and Industrial Hygienists, 1995.