Bakers' rhinitis

Diagnostic criteria, flour dust exposure, mucosal inflammation, IgE sensitization, and relation to lower airways

Torgeir Storaas

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Torgeir Storaas

Department of Otolaryngology, Head & Neck Surgery,
Haukeland University Hospital, Bergen

Department of Occupational medicine, Section of Clinical Allergology,
Haukeland University Hospital, Bergen

Department of Surgical Sciences, Section for Otorhinolaryngology,

University of Bergen,

Norway

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Abbreviations

AAAAI	American Academy of Allergy,Asthma and Immunology
ACAAI	American College of Allergy,Asthma, and Immunology
ATS	American Thoracic Society
CI	Confidence Interval
CNBI	Confederation of Norwegian Business and Industry
ECP	Eosinophilic Cationic Protein
ECRHS	European Community Respiratory Health Survey
GM	Geometric mean
HDM	House dust mite
HRT	Histamine Release Test
ICR	International Consensus Report on Rhinitis
IgE	Immunoglobuline E
ISAAC	International Study of Asthma and Allergies in Childhood
NOK	Norwegian Kroner
OA	Occupational Asthma
OcR	Occupational Rhinitis
OR	Odds Ratio
SD	Standard Deviation
SPT	Skin Prick Test
QoL	Quality of Life

Contents

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Summary

This thesis is the results of a cross-sectional epidemiological study undertaken in the period from March 2000 to January 2002 on bakery workers in 6 bakeries in Bergen, Norway. The aims were to study the consequences of different criteria for the diagnosis of occupational rhinitis (OcR), assess the prevalence of IgE sensitization, and to explore the relationships between OcR, upper and lower airway symptoms, IgE-sensitization, nasal indices of inflammation, bronchial responsiveness, and flour dust exposure. We have taken into account possible confounders such as age, gender, smoking, and baseline lung function, and we also present an alternative continuous outcome estimate of bronchial responsiveness.

Bakery workers (n=197) were subjected to interviews, questionnaires, workplace dust measurements, allergy tests, and nasal lavages with and without histamine provocation. The criteria for the diagnosis of OcR were based on the International Consensus Report on Rhinitis (ICR) from 1994. α_2-Macroglobulin and eosinophil cationic protein (ECP) were measured in nasal lavage fluid. Bronchial provocation test with metacholine was carried out according to the American Thoracic Society's guidelines. Bronchial responsiveness was expressed as $slope_{conc}$, a measurement derived by regressing the percent reduction in FEV_1 at each provocation step.

The prevalence of OcR varied between 23 and 50% depending on the diagnostic criteria used. OcR, both IgE- and non-IgE-mediated, was associated with asthma symptoms. The most frequent causes of sensitization were various species of storage mites (20%). Storage-mite sensitization was related to both OcR and work exposure (production workers versus administrative staff).

α_2-Macroglobulin, ECP, and the exudative responsiveness to histamine increased significantly with increasing workplace dust exposure ($p \leq 0.035$). Similar patterns were seen in workers with OcR and with work related rhinitis symptoms, but occupational sensitization was not a discriminating factor. Bronchial hyperresponsiveness (BHR) expressed as $slope_{conc}$ was associated with smoking ($p=0.017$) and asthma symptoms at work ($p=0.003$), but not with IgE sensitization to occupational allergens ($p=0.221$) when we also adjusted for baseline lung function. We demonstrated an association between ECP in nasal lavage and BHR in a subgroup where BHR was defined as $slope_{conc} < 3$ ($p=0.012$). No association was seen between bronchial responsiveness and current exposure level of flour dust, nasal symptoms, and a diagnosis of OcR.

Using different diagnostic criteria have considerable consequences for the prevalence of OcR. There is a strong relationship between OcR and lower airway symptoms. Storage mites maybe important occupational allergens in Norwegian bakeries. OcR and occupational dust exposure in bakery workers is associated with nasal eosinophilic exudative inflammation. In contrast, occupational sensitization is not a discriminating factor with regard to nasal indices of eosinophilic, exudative inflammation. Bronchial hyperresponsiveness measured by metacholine provocation is related to baseline lung function, smoking, work related asthma symptoms, and nasal eosinophil activity, but not to occupational IgE sensitization. The $slope_{conc}$ expression seems to be a useful continuous outcome in bronchial responsiveness testing with metacholine.

1. Introduction

The idea to make this study originates from recognition of the frequent referral of bakery workers to the department of Occupational Medicine at Haukeland University Hospital. The symptoms ranged from skin rash to upper and lower airway symptoms. Some of the workers could be relocated from their original work place in the bakery, but many were unable to continue as bakery workers altogether.

Previously there had not been undertaken any larger studies in bakeries in Norway except for some exposure measurements in solitary bakeries. The results reported by the Norwegian Labour Inspection Authority indicated rather high levels of flour dust exposure (Direktoratet for arbeidstilsynet, 2000). When we contacted the bakeries we were encouraged to carry out this investigation both by the working force, their unions, and the employers. The overall feeling in the milieu was that the time was more than overdue for an investigation that could legitimate improvements in the working environment.

It has been claimed that asthma is one of the most common work related diseases in the western world, and in many countries bakers' asthma is the most common respiratory work related disorder to be reported (Chan-Yeung & Malo, 1995; Baur 1999; Houba et al., 1998a). Bakers' asthma is also in Norway among the most frequently reported work related disorders. Leira et al. (2005) recently published that baker's asthma is the second most frequently reported occupational asthma in Norway after the potroom asthma. Due to poor reporting routines in the bakery industry the true frequency of bakers' asthma in Norway may in fact be comparable to asthma contracted in the aluminium industry where there have been active screening programs for many years. A majority of the notified cases seemed to become chronic despite medical treatment, and there was a need for earlier recognition to prevent this from happening.

We do recognize asthma as a disease with a high burden of morbidity, and with possible fatal outcome. What about the occupational rhinitis? Is it important?

The last decades several papers dealing with the aspects of quality of life (QoL) in rhinitis have been published (Juniper & Guyatt, 1991; Bousquet et al., 1994; Meltzer et al., 2001). In the ICR this has been summarized as: 'Patients with rhinitis are not just troubled by nasal symptoms. The condition impacts heavily on health-related quality of life. Patients are limited in their inability to do everyday activities, concentration is impaired, associated symptoms such as headache are troublesome, practical things such as remembering to carry a handkerchief and repeatedly blowing the nose are a nuisance, sleep is impaired, social interaction is limited and there is an impact on emotional well-being' (ICR, 1994, p.9). Furthermore, findings from a population-based survey on allergic rhinitis showed that the sick-leave was as high as, or even higher than in asthmatics, and at least 50 % had decreased performance in school or at work (Blanc *et al.,* 2001).

Most papers about QoL in rhinitis deal with allergic rhinitis in general, but we have reason to believe that these above mentioned aspects apply for the occupational acquired rhinitis as well, even though there are no studies on QoL in OcR to our knowledge. The accumulated evidence of the importance of rhinitis for QoL, and its socio-economic impact should lead to an increased apprehension of the patients with rhinitis both in general practice, but also in the occupational setting.

2. Background

2.1 Historical review of airway disease in bakery workers

Hieroglyphs and pictures from Egypt drawn 2500 years b c depict the cutting and manufacturing of the grain, and bread has been found in the Egyptian kings graves. Although we believe that the modern man has developed an increased susceptibility to mucosal irritants through the centuries of hygienic and technological development, the handling of grain and flour probably already then caused airway symptoms. From 1713 with the work "De Morbis Artificiae Diatriba" by Ramazzini we have been aware of the serious consequences dust exposure may cause in the bakery workers.

Today airway symptoms are prevalent in bakery workers. The prevalence figures published range from 14 % to 35 % in the lower airways, and from 29 % to 38 % in the upper airways (Cullinan et al.,1994; Musk et al.,1989; Houba et al., 1998b). The development of respiratory diseases in bakery workers seems to be increasing. From the Finnish Register of Occupational Diseases Reijula et al. (1994) have reported a two-fold increase in asthma, and a 5-fold increase in rhinitis in the period 1981-1991. The yearly incidence (included allergic alveolitis, asthma and rhinitis) was highest among bakers, and estimated to 3.7 per 1000. The incidence of baker's asthma in Sweden has been estimated to 0.8 per 1000 (Malmberg P,1990; Toren K, 1996). The Surveillance of Work Related and Occupational Respiratory Disease (SWORD) in United Kingdom has revealed incidence rates of baker's asthma around 1.0 per 1000 from 1992 to 1997 (McDonald et al., 2000).

The Norwegian Arent de Besche (1929) was one of the first to postulate that the underlying cause of baker's asthma was wheat allergy. In 1933 KH Baagøe, another Scandinavian researcher described both bakers' rhinitis and asthma due to 'mehlidiosynkrasie', today best translated as 'flour allergy'. Since then the possibility of an allergic reaction to specific ingredients in the working atmosphere as the main

cause of work related morbidity in bakery workers has been focused on in the research.

Allergy, as a medical entity, got a new legitimacy in 1968 with the recognition of a new immunoglobulin, IgE. This discovery is linked to the Swedes Johansson and Bennich, and Ishizaka and his group in Denver, Colorado (Bennich et al., 1968). The radioallergosorbent test (RAST) which was developed in collaboration with Wide (Uppsala), made it possible to detect specific IgE to allergens in serum (Wide et al., 1967). Since then specific IgE tests have been developed to a wide range of possible occupational allergens encountered in bakeries and confectionaries.

Houba et al., (1998b) have in their comprehensive review of the literature about occupational respiratory allergy in bakery workers accounted for more than 30 possible allergens, and the list has increased since then (xylanase: Baur et al., 1998; β-xylosidase: Sander et al., 1998). The diversity of occupational sensitizers ranges from flour (wheat, buck-wheat, rye), other baking ingredients (soy, egg), baking additives (especially α-amylase), storage mites to insects (cockroach).

The continuing work with characterization of wheat has so far revealed more than 70 possible epitopes that have the ability to bind IgE (Baur & Posch, 1998). The enzyme α-amylase emerged as a new allergen in the baking industry around 1980 (Heyer 1983; Baur et al., 1986). This enzyme has in some studies turned out to be the most important sensitizing allergen (Smith et al., 1997). Several studies have found high prevalence of storage mite sensitization in bakery workers ranging from 11-33 % (Musk et al., 1989; Cullinan et al., 1994; Houba et al., 1996a). Some authors have suggested storage mite allergens as possible occupational sensitizers, while others have concluded that these allergens should be regarded as common aeroallergens, and sensitization rather as a sign of atopy (Revsbech & Dueholm 1990; Armentia et al., 1992; Tee, 1994; de Zotti et al., 1994).

The most used definition of atopy has been sensitization to one or more common aeroallergens. Several cross-sectional studies have seen an association between atopy and occupational sensitization in bakery workers (Cullinan et al., 1994; De Zotti et al., 1994; Houba et al., 1998a). De Zotti et al. did also demonstrate a relationship between atopy and lower respiratory symptoms as did Prichard et al. (1985). However, this was not the case in Cullinan et al.'s study.

Jarvinen et al. (1979) concluded in their study of 234 bakery workers that this occupation is unsuitable for individuals with atopy. In De Zotti et al.'s study on pre-employment screening among trainee bakers (1995) they conclude that to prevent asthmatic teenagers to choose occupation as bakers is rational. In his thesis Houba (1996) points out that the prevalence of atopy in the general population is high, and the association between atopy and occupational allergy is not absolute. A substantial proportion of subjects who will develop respiratory symptoms are however not atopic (Houba, 1996). Brisman finds the selection of atopics out of bakery work to be of questionable value since the positive predictive value of having hay fever in relation to asthma was only 9 % in his study (Brisman, 1999). This is in line with the view of Nordman (1994), and Vanhanen et al. (1996) who report the predictive value of atopy for sensitization to flour and enzymes far too low to justify such a practice.

Cullinan et al. (1994) managed to show a positive relationship between flour dust/aeroallergen exposure levels and both symptoms and sensitization in bakeries. Burdorf et al. (1994) have shown how the work task in the bakery may indicate the level of exposure; the dough-maker being the most exposed. They found the following levels (as GM): Dough-makers 5.46 mg/m^3, bread-formers 2.69 mg/m^3, oven workers 1.17 mg/m^3, confectionery workers 0.58 mg/m^3, packers 0.48 mg/m^3. Houba et al. (1997a) identified the specific job of a bakery worker as the most important source of variability in inhalable flour dust concentrations, and hence a classification by job title would lead to sufficient contrast in average exposure levels for inhalable dust.

In earlier studies there have been contradictory results whether smoking promote occupational sensitization and respiratory symptoms. De Zotti et al. (1994) demonstrated smoking associated to occupational sensitization, but not to work related symptoms. Cullinan et al. (1994) found smoking not independently related to either symptoms or to a positive skin test.

2.2 Rhinitis

2.2.1 The diagnosis: definition and criteria

The problems due to a lack of standardized definitions have been addressed by several authors, both on allergic rhinitis (Ng et al., 2000), occupational allergic rhinitis (Hytonen, 1997), but also when considering rhinitis in general. As stated by Cauwenberge and Ingels in the comprehensive textbook 'Asthma & Rhinitis' by Busse & Holgate in the chapter on 'Rhinitis: spectrum of the disease': 'It is clear that there is not an accepted classification of rhinitis' (Cauwenberge and Ingels, 1995). This is followed by Sibbald and Strachan on page 32 in the same textbook: 'There are no widely agreed criteria for the diagnosis or classification of rhinitis' (Sibbald and Strachan, 1995). Mygind and Naclerio (1993) express the same concerns: 'There is no universally accepted system for the definition, classification or the terminology of rhinitis', and they point out the problems with the great variation in terminology, and lack of stringent use of several rhinitis labels.

In the initial phases of this study the International Consensus Report on the diagnosis and management of rhinitis from 1994 (ICR) was the only published paper where the issue of definition and diagnostic criteria of rhinitis had been dealt with in depth. In the ICR there appears to be two definitions of rhinitis. The first definition is: 'Inflammation of the lining of the nose, characterized by one or more of the following symptoms: nasal congestion, rhinorrhoea, sneezing and itching'. In a management algorithm at the end of the document the following symptom-based definition is

presented: ‘Two or more nose symptoms (nasal discharge, blockage or sneeze/itch) for more than one hour on most days’.

In 1998 the Joint Task Force of the assemblies of AAAAI, ACAAI and the Joint Council on Allergy, Asthma and Immunology presented their complete guidelines to the diagnosis and management of rhinitis (Dykewicz et al., 1998). In these guidelines the definitions of rhinitis and occupational rhinitis (OcR) are similar to the 1994 consensus report (ICR). As the ICR, the 1998 guidelines stress the issue of an inflammation in the membranes of the nose as the base of the diagnosis, and list the same symptoms as the ICR when characterizing the disease.

Rhinitis is an inflammation of the nasal mucosa. A key feature of mucosal inflammation is the exudation of plasma proteins such as albumin, α_2-macroglobulin and others. This process can be monitored by analysis of plasma proteins in nasal lavages (Greiff et al., 2001). Whereas low molecular weight plasma proteins such as albumin (69 kD) may be present in nasal surface secretions in high concentrations under physiological conditions, this is not the case for larger proteins. Thus, plasma proteins such as α_2-macroglobulin (720 kD) can be used to detect plasma exudation with greater sensitivity than albumin (Howarth et al., 2005).

In the review by Nathan et al. (2005) the term ‘nasal responsiveness’ is defined as the functional responses of the nasal mucosa to a variety of stimuli, both of physical and chemical nature. These reactions should be considered part of the protective function of the nose. The term ‘hyperresponsiveness’ refers to exaggerated protective responses. Since the nasal mucosa comprises several functional elements, it is important to define hyperresponsiveness as an attribute of a specific functional element of the nasal mucosa, and not as a global condition (Nathan et al., 2005). Histamine challenge to demonstrate nasal hyperresponsiveness has been used in various ways, and with a range of end-points. Hallen and Juto used stereometry to evaluate exactly the degree of swelling in the nasal mucosa after histamine challenge (Hallen & Juto, 1993; Hallen & Juto, 1994). The method of employing histamine lavages and monitor the ability of histamine to produce plasma exudation gives the

opportunity to verify nasal exudative hyperresponsiveness. Increased exudative responsiveness to histamine has previously been demonstrated in allergic rhinitis (Svensson et al., 1995).

2.2.2 Prevalence rates

Most prevalence studies deal with allergic rhinitis. In the Joint Task Force guidelines the prevalence is estimated to 10-30 % in adults, and in children up to 40 % (Dykewicz et al., 1998). In a much cited community study from London, a postal questionnaire, the prevalence of seasonal and perennial rhinitis together was 24 % (Sibbald & Rink 1991). Rhinitis was defined as a self-reported problem with sneezing or a runny or blocked nose in the absence of a cold or the flu. Data from the ECRHS study revealed a prevalence of 19.5 % of hay fever or nasal allergy in Bergen, Norway (Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey, 1996). Prevalence figures for non-allergic rhinitis vary from 15 to 60 % (Jessen and Janzon, 1989; Togias, 1993).

During the last decades a debate whether there is an actual increase in the prevalence rates both concerning allergic asthma and rhinitis in the western world has culminated in a general agreement that the rise in these atopic conditions is for real. One of the key references is the study by the Swede N. Åberg (1989) who demonstrated an increase in the prevalence of allergic rhinitis in Swedish conscripts from 4.4 % to 8.4 % between 1971 and 1981.

2.3 Occupational rhinitis

2.3.1 The diagnosis: definition and criteria

Considering the ‘anarchy’ in defining rhinitis no wonder there seems to be no consensus on the diagnostic criteria of occupational rhinitis in the literature. The

variety and lack of stringent definitions may have forced the authors of reviews to use a broad definition of OcR to make it possible to account for the different studies. For instance, Siracusa *et al.*, (2000) defined OcR as 'any rhinitic symptom reported as work related, excluded malignant diseases'.

ICR define occupational rhinitis (OcR) as: 'Rhinitis caused by exposure to an agent in the workplace'. The ICR does not give any guidelines to how this is meant to be interpreted. A common way to link the rhinitis to the work place is to ask whether the nasal symptoms subside or disappear when not at work, for instance in the weekends or at least when on holiday (Cullinan et al., 1994). De Zotti defined work related rhinitis as the presence of nasal symptoms (sneezing/itchy or running nose) during the working period (De Zotti et al., 1994). The gold standard in occupational asthma has been to perform provocation tests with the suspected agent from the work place in controlled surroundings (Vandenplas & Malo, 1997). Hytonen & Sala (1996) have stressed the importance of establishing a link between the OcR and the working environment by provocation tests, and they have given practical guidelines for this.

2.3.2 Prevalence rates in baker's rhinitis

Many authors have reported high prevalences of occupational rhinitis in bakeries ranging from 15 % to 40 % (Brisman *et al.*, 1999; Cullinan *et al.*, 1994; Houba et al., 1998).

2.4 Bronchial hyperresponsiveness

Bronchial hyperresponsiveness (BHR) has been defined as 'an exaggerated response to a bronchoconstrictor' (Sterk et al., 1993). Measurement of bronchial responsiveness permits identification of individuals with increased risk of airway disease since bronchial hyperresponsiveness (BHR) is predictive of asthmatic disease (Laprise et al., 1999). Studies have revealed increased bronchial responsiveness in

bakery workers compared to control groups (Musk et al., 1989; Bohadana et al., 1994). In the general population, BHR follows a continuous unimodal log-normal distribution (Yan *et al.,* 1985; Cockcroft *et al.,* 1983). Consequently, the separation of healthy from diseased individuals is difficult. Moreover, Josephs et al. (1990) found that some patients with a typical presentation of asthma did not present BHR, and in a group of patients followed for a period of one year, there was poor correlation between variations in their clinical state and the degree of BHR (Josephs et al., 1989). BHR is also seen in various groups of non-asthmatics, as in; allergic rhinitis, normal subjects with atopic family histories, smokers (active and passive), viral respiratory infections (Colasurdo and Larsen, 1995). Nevertheless, BHR does provide a reliable marker of one physiological characteristic associated with asthma, and according to Pearce *et al.* remains the principal validation instrument for asthma prevalence surveys in preference to questionnaire definitions (Chinn & Sunyer, 2000; Pearce *et al.*, 1998).

The most used method to summarize bronchial responsiveness measurements is the dose (or concentration) of a provocative agent sufficient to cause a predetermined percentage fall in FEV_1 compared to the baseline. The disadvantage of this method is that a majority of the subjects will not reach a sufficient fall in FEV_1 to render any information. Several methods where the bronchial challenge data are expressed as continuous outcomes have been presented (O'Connor *et al*., 1987; Kennedy *et al*., 1990; Abramson et al., 1990).

2.5 Exposure limits for flour dust

In Norway, when this study started, the highest accepted level of organic dust in the working atmosphere was 5 mg/m^3. Type of dust or which sampling method should be used was not specified. The Norwegian Labour Inspection Authority decided in December 2000 that the specific limit for flour dust should be 3 mg/ m^3 (inhalable), effectuated from the first of January 2001 (Direktoratet for arbeidstilsynet, 2000).

This new limit was mainly based on the work by Houba (1996) with a threshold level for sensitization in bakeries estimated to be: 1,0 - 2,4 mg/ m^3 inhalable.

2.6 United airways

Common pathological pathways for work related rhinitis and lower airway symptoms have been proposed. As early as in the 1960's assessment on the effectiveness of specific immunotherapy showed that there was an association between allergic rhinitis and asthma. About 50 % of the control group (no immunotherapy) of children with allergic rhinitis developed asthma within few years (Johnstone & Dutton, 1968). A relevant proportion of patients with allergic rhinitis have non-specific bronchial hyperresponsiveness (Corren, 1999), and allergic rhinitis is a risk factor for asthma development (Braman et al, 1987). There is evidence for the presence of concomitant rhinitis in 80 % of asthmatics (Slavin, 1994), and 70 % of those with perennial allergic rhinitis have asthma (Varghese et al., 2000).

The concept of the 'Allergic Rhinobronchitis' or 'United Airways' has been generally adopted (Simons, 1999; Passalacqua et al., 2000). The concept has also gained attention in occupational medicine. In the review 'Baker's asthma; causes and prevention' (1999) Baur considers the occupational rhinitis as 'a pre-stage of asthma'. Malo et al. (1997) found that the nasal symptoms preceded the occurrence of lower airway symptoms. In Finland they found that occupational rhinitis emerged at a younger age than occupational asthma, and warranted greater recognition of the occupational rhinitis (Hytonen et al., 1997). Cullinan et al. (1994) found in a prospective study of apprentices who had not previously been exposed to flour that the mean time between start of exposure to debut of respiratory symptoms was shorter for nasal symptoms compared to symptoms from the lungs, 229 days and 365 days respectively.

The support for a link between the non-allergic rhinitis to lower airway disease is far less substantial. An important paper by Leynaert et al. (1999) from the ECRHS-data

demonstrates that rhinitis is a risk factor for developing asthma not only in atopic subjects (OR 8.1, CI 5.4-12.1), but also in non-atopic subjects (OR 11.6, CI 6.2-21.9). The authors conclude that the strong association between perennial rhinitis and asthma in non-atopic subjects with normal IgE levels is consistent with the hypothesis that rhinitis is an independent risk factor for asthma. Some studies show that physical stimuli as dry, moist or cold air may elicit/evoke changes in both nasal and bronchial resistance (Fontanari et al., 1996; McLane et al, 2000).

2.7 Economical impact of occupational rhinitis and asthma

When calculating the community's costs of a disease we have to take into account direct costs like medical treatment, medicines, laboratory expenses, bandages, etc. The second aspect is the indirect costs due to the decreased performance at work, and sick-leave. In Germany as many as 1800 bakery workers annually claim compensation for baker's asthma (Baur & Posch, 1998) (Also see Introduction).

Additional indirect costs may ensue because allergic rhinitis often is a concomitant illness to other illnesses. For instance, the costs are 46 % higher if an asthmatic in addition suffers from allergic rhinitis (Yawn et al., 1999). All these aspects are accounted for or mentioned when the Joint Task Force in US has estimated the cost of allergic rhinitis based on direct and indirect costs to be 2.7 billion dollars for the year 1995, exclusive of costs for associated medical problems such as associated sinusitis and asthma (Dykewicz et al., 1998). The annual cost of lost productivity as the consequence of allergic rhinitis and its therapy with the over-the counter sedating antihistamines has been estimated to be more than 4 billion dollars (Fireman, 1997). The costs related to allergic rhinitis in 1993 in Sweden amounted to 236 millions SEK as direct costs, and 283 millions as indirect costs. If the total costs of allergic rhinoconjunctivitis, asthma and allergic eczema were summed up, this would amount to 5.6 billions SEK, which is comparable to the studies from North America (European Allergy White Paper, 1997).

There are to our knowledge no cost analyses of baker's respiratory diseases in Norway. We lack good registers on occupational diseases, and only information on group level is recorded. According to one of the reports from the National Insurance Organisation from 2001 the compensations (NOK) for occupational diseases in the food-industry in the time period 1991-99 were:

1. Intoxications or other chemical exposures approx. 12.0 millions NOK

2. Allergic and other skin diseases approx. 9.0 millions NOK

3. Lung diseases caused by dust approx. 6.6 millions NOK

3. Aims of the study

The objectives of the present study on bakery workers were to:

1. Explore the consequences of different criteria for the diagnosis of occupational rhinitis.

2. Assess the prevalence of occupational rhinitis, lower airway symptoms, and IgE-sensitization, and their relationships taking into account known risk factors.

3. Use indices of inflammation in nasal lavage to characterize the occupational rhinitis in bakery workers, the indices being:
   3.1. α_2-Macroglobulin
   3.2. ECP
   3.3. α_2-Macroglobulin after Histamine challenge

4. Assess bronchial responsiveness by a tidal breathing method and metacholine provocation, and present the bronchial responsiveness as a continuous outcome. Relate this outcome to baseline lung function, sensitization, smoking, a diagnosis of occupational rhinitis, lower airway symptoms, and nasal indices of inflammation.

5. Measure the flour dust exposure level in the bakeries, and relate the exposure level to a diagnosis of occupational rhinitis, lower airway symptoms, nasal indices of inflammation, and bronchial responsiveness.

6. Investigate the relationship between upper and lower airways using the above mentioned indices of disease and risk factors.

4. Material & Methods

4.1 Study design

In 1999 a study in 6 bakeries in Bergen on the West Coast of Norway called ”Diagnosis and prevention of airborne allergy in bakers” was launched. The study was a joint project by the departments of Otolaryngology, Head & Neck Surgery and Occupational Medicine, and the Laboratory of Clinical Biochemistry at Haukeland University Hospital in Bergen, and the department of Otolaryngology/Allergy Research Lab at the University Hospital in Lund, Sweden.

Prior to the main study a pilot study was undertaken. This involved 208 bakery workers with a response rate of 89 % (186 of 208), and was done in collaboration with the health services used by the bakeries. Each participant completed a questionnaire, and blood tests were taken to test for total IgE, phadiatop, specific IgE to flour, and α-amylase (Storaas et al., 2000).

From the initial cohort of 208 bakery workers in the 6 bakeries 197 were eligible to participate in the main study which forms the basis of this thesis. The response rate was 93 % (183 of 197). Thirteen did not want to or could not participate, and one employee did only the bronchial challenge test. The study design was cross-sectional. However, preparations have been made for a follow-up in a 10 years frame.

All employees in the 6 bakeries were recruited, and comprised not only production workers (dough makers, bread formers, oven staff, confectionary staff), but also packers, cleaners, transport staff and administrative personnel.

Following interviews, questionnaires, allergy tests and workplace dust measurements, the workers were subjected to nasal saline and histamine lavages. In addition the workers were subjected to bronchial provocation tests with metacholine. The study was conducted throughout the year, except for the nasal lavages which were carried out outside the pollen season.

4.2 Subjects

Demographic data are presented in Paper I.

Table I: Information on number of employees and characteristics of production in the 6 bakeries:

Bak-ery	Number	Type of production	Confectio-nary	Level of automation	Yearly consume of flour (% wheat flour)
A	77	Trad[1], mainly bread	Yes	High	5 250 tons (63%)
B	44	Trad[1], varying production	Yes	Moderate	1 000 tons (60%)
C	18	Mainly buns/hot-dog bread	No	High	2 000 tons (80%)
D	24	Trad[1]	No	Moderate	890 tons (70%)
E	19	Trad[1]	Yes	Low	180 tons (60%)
F	15	Thin pancakes	No	High	470 tons (Nearly 100%)
All	**197**				

1) Traditionally: Production of different types of bread (fine/granulated), rolls, buns and Danish pastry

4.3 Questionnaire

A self-administered questionnaire and a work task scheme with information on primary and secondary work tasks in present and previous employments in bakeries were completed by the bakery workers. Further details are outlined in the papers I-III. The work task scheme is a modification of a scheme received from Jonas Brisman, Malmø. The questionnaire and the work task scheme are presented in the Appendix in Norwegian and in an English translation.

4.4 Interview

As accounted for in the method-chapters of the 3 papers (I-III), the interviewer was blinded for the results from the questionnaires, and the occupational dust exposure data. To standardize the interview a register scheme was used.

In paper I we defined 4 categories of OcR (Table II in Paper I). Each category of OcR were further divided in IgE- mediated and non-IgE-mediated occupational rhinitis based on the documentation of sensitization to one or more of the occupational allergens (Johansson et al., 2001). In paper II and III the categories OcR-I and OcR-II were used.

4.5 Documentation of IgE-sensitization

Three supplementary methods were used to evaluate sensitization to occupational, and common airborne allergens; serum IgE, skin prick test (SPT), and Histamine release test (HRT). Occupational sensitization was defined as a positive test to at least one of the following allergens: wheat, α-amylase, oat, barley, rye, soybean, storage mites (*A. Siro*, *L. Destructor*, *T. Putrescentiae*), the mould *Clad. Herbarium* or the cockroach *B. Germanica.* The 16 allergens tested were chosen based on literature studies, and the knowledge of the baking traditions in Western Norway. In the skin prick test the following allergens were tested: wheat, oat, barley, rye, α-amylase, storage mites (*A. Siro*, *L.Destructor*), the mould *Clad. Herbarium,* and timothy (Skin tests in type I allergy testing Position paper, 1989). Further details are found in the material and method chapter of paper I.

4.6 Nasal lavage

In paper II and III are presented results from nasal lavages with and without histamine carried out using a pool-device (Greiff et al., 2001). This method has been

validated through several papers from the research group in Lund, and by others, for instance in Lodz, Poland. (See the discussion chapter). The method is outlined in the material and method chapter in paper II and III.

4.7 Lung function tests

Spirometry was done as part of the bronchial metacholine provocation test. The expression PC_{20} was defined as the provocative concentration of metacholine required to reduce FEV_1 by 20% from baseline FEV_1. Since the common used expression of bronchial responsiveness, PC_{20}, yielded data on less than approximately 30 % of the bakery workers, an alternative expression of bronchial responsiveness was constructed, the $slope_{conc}$. In the appendix of paper III the PC_{20} results were compared to the $slope_{conc}$ results. The methods of the lung function tests are described in the material and method chapter of paper III.

The use of different reference values makes comparisons between BHR studies difficult. At least it should be stated which one is used. In Norway it is reasonable to use the reference values by Gulsvik et al. (the last version published in 2001) which have been shown to be at a higher level than the European Community for Coal and Steel recommended reference values (Thorsen et al., 1990).

4.8 Exposure measurements

As accounted for in more details in paper II the dust exposure was measured using personal borne Gelman total dust samplers. Only a few of those workers asked to wear the equipment declined to do so. It was not possible to put through the flour dust measurements at the same time as the clinical investigations on the bakery workers in each bakery. All the flour samples were analysed by the same person (TVD).

4.9 Statistical methods

Statistical analyses were performed by SPSS for Windows (SPSS, Chicago, IL). Odds ratios (OR) were calculated with corresponding 95% confidence intervals (CI). Analysis of relationships between symptoms, clinical signs, test results, and dust exposure were performed with both crude OR and multiple linear and logistic regressions where we adjusted for the potential confounders: age (or working years), gender and smoking habits. In paper III the analyses of bronchial responsiveness were also adjusted for percent FEV_1 of predicted. To test linear trend of $slope_{conc}$ in paper III linear regression was done through analysis of variance.

With sparse numbers in some of the cells, an exact method (StatXact) was used in paper I to calculate the exact confidence interval for the crude OR. The nasal lavage data did not follow a normal distribution, and non-parametric tests were used, and the corresponding tests were used (Kruskal Wallis test, Mann Whitney U-test, and Wilcoxon signed rank test). Nasal lavage data were thus presented as medians with inter quartile ranges.

5. Results

5.1 The consequences of different diagnostic criteria for OcR

In the first paper we explored the consequences of different criteria for the diagnosis occupational rhinitis (OcR) when basing the criteria on the consensus report on rhinitis published in 1994 (ICR, 1994). We found that the prevalence may differ from 23% to 50% depending on how strict the criteria are set, and this is more than a two-fold increase when the least strict criteria were used.

5.2 Associations with OcR

The diagnosis of OcR, both IgE-mediated and non IgE-mediated, was strongly associated with asthma symptoms (Paper I).

OcR was also found to be associated with occupational sensitization, but only weakly, and not when using the most strict criteria for the OcR diagnosis (Paper I).

In paper II an association of OcR with current flour-dust exposure in a dose-response manner was shown. We also presented in paper II that former and current dough-makers were found to have a higher risk of contracting OcR than never dough-makers.

OcR was found to be associated with indices of inflammation (ECP, and α_2-macroglobulin both before and after histamine challenge) (Paper II).

5.3 Indices of inflammation in nasal lavage

The use of nasal lavage revealed a dose-response association of the indices of inflammation (ECP, and α_2-macroglobulin before and after histamine challenge) with

increasing levels of current flour-dust exposure, except for those with the highest exposure (> 4 mg/m^3) (Paper II).

Both α_2-macroglobulin and ECP were clearly raised in subgroups with nasal symptoms with either improvement in vacations or with a trigger factor for the nasal symptoms in the working environment (Paper II).

In paper III we demonstrated a relation between bronchial hyperresponsiveness and increased levels of ECP in nasal lavage in a small group of the bakery workers. The same group showed a tendency towards higher levels of α_2-macroglobulin at baseline and after histamine challenges (Paper III).

We did not find an association between occupational sensitization and the indices of inflammation in the nose (Paper II). Higher levels of α_2-macroglobulin (but not ECP) were seen in those with atopy (sensitization to common aeroallergens) (Paper II).

5.4 Sensitization to occupational aeroallergens

The prevalence of work related sensitization (occupational sensitization) varied between 38% to 45% in the different categories of OcR.

Sensitization to storage mites was common (20%). Only half of those with storage mite sensitization were also sensitized to common house dust mite (D. Pteronyssinus) (Paper I). We found the sensitization to storage mites associated with OcR, and storage mite sensitization was more common in the production workers (23%) than in the administrative staff (6%) (Paper I).

5.5 Workplace dust exposure

Workplace dust exposure was high in all the bakeries investigated, highest in the dough-making area, lowest in the administration (Paper II).

Lower airway symptoms with work relation were found to be associated with workplace dust exposure when comparing the groups below and above 1 mg/m^3 (Paper II).

In paper I we presented higher prevalences of asthma symptoms, and other lower airway symptoms in our bakery worker group compared with a population based study from the same county using exact the same questions.

Also a relation between workplace dust exposure to OcR and nasal indices of inflammation was shown (see above) (Paper II).

5.6 Bronchial responsiveness measured after metacholine challenge

We expressed the bronchial responsiveness after metacholine challenge as a continuous outcome based on regressing the percent fall in FEV1 at each metacholine concentration step. The expression was named 'slope$_{conc}$', and was found to have a normal distribution in the study group, and to correlate with PC_{20} (Paper III-Appendix).

Slope$_{conc}$ was found to be associated with baseline lung function, smoking, and lower airway symptoms. The association with occupational sensitization was lost when adjusting for baseline lung function.

No association was seen between slope$_{conc}$ and current exposure level of flour dust, number of working years in a bakery or a history of dough-making.

As mentioned above we found an association of bronchial hyperresponsiveness (slope$_{conc}$< 3) with nasal ECP.

5.7 The relationship between upper and lower airways in the bakery workers

Based on the interview we found that the work related nasal symptoms emerged earlier than did lower airway symptoms (Paper I). As mentioned above, both interview and questionnaire based OcR were found to be related to asthma symptoms (Paper I). In paper III we presented higher ECP levels in nasal lavage in those with bronchial hyperresponsiveness (see also above).

Despite the seemingly strong association of OcR with asthma symptoms (Paper I), we were not able to show a relationship between OcR and bronchial responsiveness measured by metacholine challenge (Paper III).

6. Discussion

6.1 Study design and methods

6.1.1 Cross-sectional vs. longitudinal

In a cross-sectional design all information is collected at the same time. A longitudinal study follows the subjects for a longer time period, often with several contacts, and is especially more powerful when looking at causal relationships. However, the disadvantage with longitudinal studies is that they are more laborious and expensive.

In all observational studies, we have to be cautious in the interpretation of the results. Especially in cross-sectional studies we have to restrain ourselves to only make assumptions of associations, and avoid firm etiological considerations based on the data. However, cross-sectional studies have made important contributions as hypothesis generating instruments. If several cross-sectional studies point in the same direction this may have some weight in causality issues as well.

6.1.2 Sample selection

Our baker cohort consists of workers from 6 bakeries that differ in the number of employees, production methods, and degree of automation, but also to some extent in the spectrum of products. We have intentionally not included small bakeries (1-3 employees), but bakery E (Table II) is very similar to a smaller bakery concerning product spectrum, production methods, and degree of automation, although not in number of employees. All put together our cohort should be quite representative for most of the bakery workers in Norway.

6.1.3 Control group

In our study no external control group was used. This matter was discussed with the Centre for Clinical Research when we were planning the study, and we decided not to include a control group. The selection of a suitable control group is quite difficult,

and since we have included all workers in the six bakeries in our cohort, varying degrees of exposure were represented. Thus, the cohort comprises the whole range of different work tasks, and perhaps most important; the cohort comprises employees ranging from those who are scarcely exposed to flour dust at all (administrative personnel) to those with the heaviest exposure load (dough makers). In the majority of our analyses we chose the group with an exposure level of less than 1 mg/m^3 (among those packers and administrative personnel) as our control group.

6.1.4 Potential bias

Several types of bias may occur in cross-sectional studies. In this study in occupational medicine, we are especially concerned about a possible 'healthy worker' effect. The ones who get sensitized to occupational allergens or get work related symptoms/diseases will be prone to quit the job, and leaving behind a 'survivor population'. This will inevitably lead to an underestimation of the effects of exposure and preclude the dose-response relationships we would want to study. In our case we have proposed that those working with the highest flour dust exposure level, which is > 4 mg/ m^3, may be an example of a survivor population. In paper II we have described the rather peculiar fall in indices of inflammation in this group compared to the groups with less exposure where there seems to be a dose-response relationship (alternatively this may be the result of misclassification.)

The results from a questionnaire will be subjected to recall bias. Those with a heavy load of symptoms will tend to remember more than those with fewer symptoms. The ERS-task force state that questionnaires may be subjective and the level of awareness of the condition in the community may influence the pattern of response (Joos et al, 2003). On the other hand, Gordon et al. (1997) found that screening questionnaires may lead to an underestimate of the prevalence of asthmatic symptoms in bakery workers.

We cannot rule out the possibility of some degree of investigator bias in the interview, perhaps especially concerning the questions whether nasal or lower airway symptoms appeared first.

6.1.5 Allergy tests

As shown in Paper I the sensitivity of Histamine release test to occupational allergens was rather low compared to specific IgE, and to skin prick testing regarding some of the common allergens as well. The Histamine release test is well validated, and we have no explanation for this lower sensitivity. We have not done any systematic analysis of this matter so far.

6.1.6 Flour dust measurements

At the time when this study was prepared, the new EU standard for sampling airborne particles in working atmosphere had been accepted, but not fully implemented (NS-EN 481, 1993). There were several different sampling devices in use, but still none had gained universal approval. In Norway the standard cassette with 25 mm Millipore filter had been in use for many years. These were the main reasons for our choice of the Gelman standard cassette.

By immunoassay techniques it has become possible to quantify wheat and a-amylase allergens in the flour dust (Heederik et al., 1999). Some studies have concluded that the great variation in the amount of aeroallergens in the flour dust necessitates exposure assessments not only at dust level, but also by allergen quantification (Houba et al., 1996a; Burstyn et al. 1999). Nieuwenhuijsen et al. (1994) showed moderate correlation between flour dust concentrations and wheat allergen; whereas Houba et al. (1997b) found poor correlation to α-amylase. However, Cullinan et al. (2001) found that the overall dust exposure also reflected exposure to occupational allergens. The analyses in our study are based on the latter assumption.

6.1.7 Nasal lavage

Nasal lavage is well tolerated, rather simple and rapid to perform, and has been extensively used in experimental/laboratory research to elucidate the luminal cell recruitment, cell activation, and plasma protein extravasation in the nose, both under natural challenge conditions, but also when using a wide range of different stimuli (Howarth et al., 2005). The repeatability of the nasal response to histamine has been

evaluated under laboratory challenge conditions. Svensson et al (1989) found that the vascular response, as measured by TAME esterase and albumin, was reproducible and repeatable. And the eosinophil response, monitored by ECP levels, is repeatable in response to allergen challenge (Howarth et al., 2005).

The method has been less used under clinical and epidemiologic circumstances, and Howarth et al. (2005) report that the sources of variability and the repeatability of the findings are poorly substantiated under field conditions. In our study approximately half of the nasal lavages were done in the bakeries, the other half in the laboratory at Haukeland University Hospital. The travel time between the bakeries and hospital was from 5 to 45 minutes. When analyzing the data split by where the nasal lavage took place we found a tendency to higher values when the lavages were done at the laboratory, but not reaching a significant level. And we did not find any differences in the results of the analyses done in Paper II when splitting the data likewise.

We found that the nasal pool device was well tolerated by all participants in our study. By this technique known concentrations of agents (for instance histamine) may be brought into contact with a large and defined area of the nasal mucosal surface. Simultaneously, the surface exudations/secretions of the same nasal mucosa are effectively sampled (Greiff et al., 1990). The main problem experienced by some of the participants was in sustaining the pressure on the container through the 5 minutes before releasing the lavage fluid into the collecting funnel.

6.1.8 Bronchial metacholine challenge

Chinn & Schouten (2005) have proposed alternative methods, including a dose-response slope method, to strengthen the power when analysing bronchial provocation measurements. We have modified a method used by Chinn et al. (1997) in the ECRHS-studies since we have done metacholine provocations with use of the Wright nebuliser, and not by a dosimeter method. To assess the carry over effects between provocations, the cumulative concentration of all prior concentrations, as well as the previous and the present concentrations, was used at each step as

alternative methods. The BHR calculated by these methods was close to the original one as presented in Paper III.

6.2 Statistics

6.2.1 General considerations

In several of the regression analyses done we present rather wide confidence intervals. This should lead to cautious interpretation of the results. The nasal lavage data were too skewed to be eligible for log transformation to reach normality, and as a result we have used non-parametric tests in all analyses where the nasal lavage data are included.

6.2.2 Confounders

The age distribution in our cohort made this parameter sometimes influencing the statistical analyses quite heavily when testing for significance. Is it really plausible that age has a true influence on the issues we have been studying? Anyway, since age has 'traditionally' been reckoned as a confounder we have tried to incorporate this parameter in all analyses when possible.

The role of smoking in the development of occupational asthma (OA) is still not clarified. In their recent review on the matter, Siracusa et al. (2006) state that there is little evidence of an increased risk of OA in workers who are smokers. In an ATS/ERS report about key questions and needs in occupational asthma Tarlo & Malo (2006) ask: why does smoking appear to increase the risk of sensitization to some agents, but reduces the risk for sensitization to others? In a longitudinal study by de Zotti & Bovenzi (2000) they found the risk of developing occupational sensitization greater in smokers, but not significantly, and smoking was not a determinant for the incidence of work related respiratory symptoms. We have not presented data for smoking in relation to either sensitization or respiratory symptoms, but incorporated

smoking as a possible confounder in the regression analyses. We did find a positive association to BHR (Paper III).

6.3 Occupational rhinitis

6.3.1 Definition and classification

Our call for a new consensus on the definition of OcR in Paper I is supported in the review about the dilemma of OcR by Hellgren et al. (2003). They put it very strongly, concluding with the phrase: 'There is an urgent call for standardization in the definition and diagnosis of occupational rhinitis'. Castano et al. (2006) have recently given more direct support to our call for a redefining of rhinitis and OcR by letting our paper be their starting point in a letter to the editor concerning the same matter. In their ending remarks they put forward that the revision of the definition of occupational rhinitis should start with the revision of the definition of rhinitis in general.

The ICR has several weaknesses, and some of them are mentioned in our Paper I. There are 2 definitions of rhinitis in ICR with limited recommendations on how to understand the relation between them, and how to use them. The first, which probably is the most commonly cited and accepted definition of rhinitis, define rhinitis as: 'inflammation of the lining of the nose, characterized by one or more of the following symptoms: nasal congestion, rhinorrhea, sneezing and itching'. In the before mentioned letter to the editor Castano et al. (2006) criticize that the symptoms all have the same weight, and refer to Ng et al (2000) that found runny nose and sneezing, and thereafter sniffing and impaired sense of smell ranking as the most important symptoms in allergic rhinitis. There have also been raised critical remarks to the criteria of inflammation as the only histopathological finding in rhinitis in view of studies showing remodelling of the upper airways in allergic rhinitis (Salib & Howarth, 2003; Castano & Theriault, 2006). This theory is not well established so far, and inflammation should still serve as the hallmark of rhinitis.

Since there currently is no agreement on an international standard method to objectively diagnose nasal inflammation, symptom evaluation alone has been extensively used in the diagnosis of OcR, as we did. But there are problems with the symptom related definition in ICR as well. We have in Paper I questioned the claim of a certain time length of the symptoms ('more than one hour most of the days'). It is understandable as a way of distinguishing the true rhinitis from the frequent experience of some nasal symptoms in the normal population (see later), but it showed to be a difficult criteria to cope with in our bakery worker cohort. Additional symptoms than those mentioned in the ICR may also be very relevant in OcR, as crust formation in ship-builders, bakers and paper workers, increased nose bleeding in wool-cotton workers and impaired sense of smell in woodwork teachers, factory workers and tank cleaners (Welch et al., 1995; Brisman et al.1998; Hellgren et al., 2001; Love et al., 1988; Ahlstrøm et al., 1986; Corwin et al., 1995; Holmstrøm et al., 1995).

The high prevalence of rhinitis in the general population (see Background) has recently been confirmed. In a population-based study on non-infectious rhinitis the overall prevalence was 40 %. The non-infectious rhinitis entity represents both allergic and non-allergic rhinitis, and the true prevalence was probably even higher than 40 % (Hellgren et al., 2002). Moreover, merely as part of a normal defence mechanism, daily nasal symptoms are experienced in 40 % of the normal population (Eccles, 1995). These facts underscore the importance of establishing a link to the work-place when suspecting OcR.

Hytonen & Sala, (1996) state that a provocation test is required to confirm the causality between the rhinitis and the work exposure. It was not within the possible scope of our investigation to do provocation tests on all who reported nasal symptoms as work related. We tried to establish the relationship between disease and workplace more firmly by additional questions in the questionnaire and interview. The relationship to the work place was characterized by at least one of the following: an occupational trigger factor, improvement of nasal symptoms during

vacations/weekends, or no history of nose-problems before start of employment. In ICR occupational rhinitis is defined as: 'Rhinitis caused by exposure to an agent at work'. To be able to link the nasal symptoms with the working conditions we found it necessary to implement the question of a trigger factor in our definition of OcR. The use of a trigger factor from the work place environment as part of the diagnosis of OcR could be criticized because inclusion of an exposure factor as part of the definition of the health effect may bias the assessment of exposure-health effect relations. The trigger factor will in most cases also be the inducer of the rhinitis, and including the trigger factor in the diagnosis may lead to an over-estimation of the health-effect. When analysing the relation between exposure level of total dust and nasal symptoms with improvement in vacations as health-effect, we found the same increasing prevalence of the health-effect by increasing exposure, and with an odds ratio if exposure level ≥ 1 mg/m^3 vs. < 1 mg/m^3 as OR: 4.67 (CI 2.26-9.65), adjusted for age, gender, and smoking status.

The classification of OcR in the ICR has also been criticized. Hellgren et al. (2003) point out that OcR is classified as 'Other', next to allergic and infectious rhinitis although allergy often is an important mechanism behind OcR. The Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology classifies OcR under both the allergic and non-allergic rhinitis categories (Dykewicz et al., 1998).

An important paper published in 2006 proposes a quite new classification of OcR (Castano & Theriault, 2006). They take advantage of the work done with the classification of occupational asthma, and divide rhinitis at the work place in three main categories; 1) OcR, 2) Work-aggravated rhinitis and 3) Rhinitis-like conditions. The latter refers to certain specific exposures at work that generate symptoms mimicking rhinitis, but where the exposures do not give rise to inflammation in the nasal mucosa. The second category is in line with our proposal in Paper I. The OcR-category is further divided in immunological and irritant-induced (non-immunological) OcR. The authors comment that the high molecular weight agents (as in the bakery industry) mainly produce IgE-mediated OcR in contrast to the low

molecular weight agents. But the latter compounds may combine with a protein to form a hapten-protein conjugate (isocyanates, anhydride acid, platinum salts) that can behave as an antigen and induce IgE-formation.

An improvement of the classification could be to subdivide the immunological OcR in IgE-mediated and non-IgE-mediated. It is then easier to find a place for our bakery workers with OcR, no IgE sensitization, but still with indices of mucosal inflammation. They may very well have an immunological induction, and may not fit in the irritant-induced/non-immunological category as we know so far. These bakers may well resemble the 2 of 36 symptomatic bakers Walusiak et al. (2004) found with positive specific challenge test (significant increase in the proportion of eosinophils and permeability index in nasal lavage), but with negative skin prick testing and specific IgE. A deduction of this may be that a positive specific challenge test may not always signify an IgE-mediated mechanism.

Castano & Theriault also want to redefine rhinitis, and thereby also OcR. They maintain the importance of being able to objectively assess the physiological change in the nose that may be attributed to the work environment. And they further maintain that nasal patency is suitable since inflammation leads to nasal obstruction, and good, valid methods to assess this are available. In our study we experienced Nasal Peak Inspiratory Flow to be easy to use and well tolerated. This method is well validated, and recommended in a recent review (Nathan et al., 2005).

The new classification may form the base in a consensus on OcR. Castano & Theriault's proposal of using an objective measure in defining rhinitis is also very good. They do not find it possible to use nasal hyperresponsiveness as the objective measurement, but this idea should be further explored, as well as the use of nasal lavage to assess inflammation. In Paper II we showed with nasal lavage techniques that it is possible to assess the inflammation in OcR, and also to differentiate objectively between workers with OcR and healthy workers without nasal symptoms.

However, this is on group level, and we lack a standardized procedure with population based reference values of the indices of inflammation to make these techniques available to clinical practice. Perhaps the Histamine challenge to assess nasal hyperresponsiveness would be more suitable in this respect. The end point could be the percentage rise of α_2-macroglobulin from the prechallenge value. Nitrogen-Oxide (NO) measurements may in the future be another way to assess nasal inflammation at the individual level (Folkerts et al., 2001; Howarth et al., 2005).

Since inflammation is difficult to assess, especially in an occupational setting, we need a substitute representing this ubiquitous feature of rhinitis in epidemiologic studies. Perhaps our results may point out some key questions in this regard? Both the questions: 1) nasal symptoms at work with improvement in weekends/vacations, and 2) nasal symptoms at work worsened or triggered by a factor in the working environment were able to single out a group of the bakery workers with significant higher levels of the indices of inflammation.

In the future a definition of OcR could be based on some absolute requirements objectively assessed, and combined with 1 or 2 nasal symptoms from a list. Different weighting of the symptoms may be suitable. Some evidence of work-relation has to be mandatory. A preliminary suggestion is presented:

A: Inflammation confirmed by

- A1: nasal patency measurements (see C1) or
- A2: nasal hyperresponsiveness after Histamine challenge or
- A3: nasal NO

B: List of work related symptoms, with weighting

C: Work relation:

- C1: A predetermined fall in nasal patency measurements at work in contrast to not at work or
- C2: Positive nasal provocation test or
- C3: NO-test at work/not at work

6.3.2 Mucosal inflammation in occupational rhinitis

Nasal lavage may be a way of monitoring the airway inflammation in bakery workers. Our nasal lavage data have given evidence for the nasal complaints of the bakery workers to be originating from patophysiological processes in the nasal mucosa, and that they are related to current flour dust exposure. We have been able to link the nasal symptoms to objective measurements, and thereby verify these subjective complaints.

In the present study, α_2-macroglobulin was employed as a plasma exudation tracer. Greiff et al. (2003) have previously shown that lavage-fluid levels of this particular protein accurately reflect plasma exudation at nasal airway inflammation. Howarth et al. (2005) states that many mediators may act on the nasal vasculature to promote plasma protein exudation, and that measurement of a marker of this process, such as α_2-macroglobulin, should provide a single integrated measurement of inflammation that reflects the underlying tissue processes. And they also state that the plasma exudation response in humans may be regarded as specific to inflammation.

As mentioned in a previous section the nasal lavage method has been less used in clinical and epidemiologic studies. Of nasal lavage data in bakery workers we have, in Paper II, discussed the studies by Brisman et al. (1998) and by the research group in Lodz, Poland (Gorski et al., 1998; Walusiak et al., 2004). The first was a case-control study with few participants, in the second the participants were recruited from a hospital out-patient clinic. The third was a follow-up/prospective study of apprentices in vocational training in bakeries. We are not aware of any other nasal lavage investigations in bakery workers that resemble a field study, and in which all workers in the bakeries were included in the recruitment procedure.

One of the reasons why we were able to demonstrate plasma exudation at workplace exposure was because we employed a very sensitive plasma exudation tracer. α_2-Macroglobulin is one of the larger plasma proteins, with a molecular weight of 725 kD, compared to for instance an often used tracer, albumin, of 66 kD. Albumin may

derive from glandular secretion, and therefore may be present in nasal surface secretions in high concentrations under physiological conditions.

It has previously been shown that nasal histamine challenge induces plasma exudation (Greiff et al., 2003). Such an exudative hyperresponsiveness has previously been shown to be a feature of nasal airway inflammation in allergic rhinitis (Svensson et al., 1995; Greiff et al., 2001). An increased responsiveness to histamine was also reported by Gorski et al. in their study where subjects with occupational rhinitis responded with greater increases in the "permeability index" compared with healthy subjects (Gorski et al., 1998).

Eosinophilia has been reckoned as a hallmark both for asthmatic inflammation, and for untreated allergic rhinitis (Gaga et al, 2000; Howarth et al., 2005). We have presented results indicating that there may be high levels of ECP also in non-IgE mediated OcR (Paper II). In our study we also found higher levels of nasal ECP in a subgroup of workers with BHR (Paper III). Here again we could not distinguish between sensitized and non-sensitized, resembling the findings in OcR. In the study by Gaga et al. (2000) they found higher eosinophil counts in nasal mucosal biopsies both in those with asthma alone and those with asthma together with rhinitis compared to the healthy control group. All participants were non-atopic. Furthermore, there was a significant correlation between eosinophil cell counts in the nasal and bronchial biopsies. They concluded that eosinophilia in the nasal and bronchial mucosa was a feature of asthma, and not related to atopy.

ECP may be elevated also in infective rhinitis as shown in the follow-up study of children in Austria where Wojnarowski et al (1998) found the highest ECP nasal lavage concentrations in those with purulent rhinitis at the time of the lavage, followed by those with serous rhinitis, and with the lowest levels in those without rhinitis. In this comparison they did not find atopy to influence the results. To conclude with a question: Is eosinophilia in the nasal mucosa a feature not only of allergic rhinitis, but for at least some types of non-allergic/non-atopic rhinitis as well, and that these considerations may be extended to OcR?

6.3.3 Sensitization and occupational rhinitis

IgE-mediated allergy to wheat and other ingredients and organisms encountered in the bakeries has been the main culprit for the baker's respiratory problems. However, we have reason to believe that other mechanisms also contribute, if not otherwise by the simple fact that less than 50 % of symptomatic workers actually are found to be sensitized in spite of extensive allergy testing. And we were not able to see any difference between sensitized/not sensitized regarding high and low levels of inflammation markers in nasal lavage (Paper II).

Surely we can't completely rule out that there may still be allergens to detect and characterize in the bakery environment. However, the last allergens to be discovered, the enzymes xylanase and β-xylosidase, have so far not shown to account for more than a minor part of the affected individuals with symptoms (Baur et al., 1998; Sander et al., 1998). And these enzymes seem to often have cross-reactivity to the more potent sensitizing, and well characterized enzyme α-amylase, although not always (Merget et al., 2001; Baur, 2005) Approximately 20-25 % of symptomatic bakery workers are sensitized to this allergen, and Brisman *et al.* (2004) found in a prospective study that 8 % of the bakery workers developed IgE antibodies to α-amylase within a period of 3 years, many of them suffered from eye/nose and/or chest symptoms. In our cross-sectional study we found a prevalence rate of 7 %, and both wheat and storage mites were more prevalent (Paper I).

Since the start of this study several papers confirming atopy as an important determinant for occupational sensitization and development of respiratory symptoms have been published (Walusiak et al, 2002; Walusiak et al., 2004; Gautrin et al., 2002). Also in our study there was an association between atopy and sensitization to the occupational allergens tested for with an odds ratio of 6.50 (CI 3.23-13.31). These results are published in a report to the CNBI Working Environment Fund (Storaas et al., 2002). We did not find an association between atopy and OcR or lower respiratory symptoms (unpublished data), neither to bronchial responsiveness (paper III). In the study by Walusiak *et al.* (2002) they concluded that the positive predictive

value of SPTs in atopic individuals starting vocational training was too low to justify prohibition of vocational training or work as bakers. But they stressed that atopic persons should be informed about their increased risk of developing occupational disease, and that this group need medical screening more often than others. In the paper from 2004 Walusiak et al. found that most of the work related respiratory symptoms among trainees were related to a specific sensitization, and they advocate that SPT to common and occupational allergens should be performed in apprentice bakers before starting vocational training. We do not fully agree since we have shown that the non-IgE mediated rhinitis is as prevalent as the IgE mediated, and also reveals increased levels of indices of inflammation in the nasal mucosa. Moreover, our data indicate that sensitization may not be the main determinant for bronchial hyperresponsiveness. We will argue that perhaps more important than pre-employment screening is the monitoring of respiratory symptoms in the bakery workers, for instance by yearly questionnaires or interviews. Emergence of respiratory symptoms, both upper and lower, should prompt further investigations including allergy tests, assessments of exposure hazards, and a plan for a close follow-up. This should go together with a continuing work for lower exposure levels of flour dust in the bakeries.

As discussed previously, also non-allergic reactions are involved in both baker's asthma and rhinitis (Nieuwenhuijsen & Burdorf, 2001). Irritative gases as NO, NO_2, acetaldehyde, formaldehyde, and acrylaldehyde may also contribute to the load of respiratory symptoms in bakery workers (Radandt, 1995). The clinical relevance of these gases in bakeries has not yet been evaluated (Baur & Posch, 1998). There are also concerns regarding the possibility of a role for endotoxin and β-glucans in the bakeries. We are not aware of any published studies in bakery workers so far.

We found in our study a high prevalence of storage mite sensitization compared to an investigation from the general population in Stavanger, Norway, and Gotland, Sweden (Finsnes, 1995; Hage-Hamsten & Johansson, 1998). Only half of these bakery workers had also HDM sensitization (Paper I). But we have to be cautious in

the interpretation of these findings, and about the possible impact on the baker's morbidity. We do not know the sensitization rate in the general population in Bergen, and we need to clarify whether there actually is storage mites present in the bakeries. Ideally we should also have done provocation tests with storage mite allergens in the symptomatic and sensitized individuals.

To directly compare our prevalence figures with the investigation done by Finsnes in Stavanger is not quite fair since we used a larger spectrum of allergy tests. And it is possible we would have found some more HDM sensitized among the storage mite sensitized if we also had done Histamine release and skin prick testing for HDM as we did for storage mites.

In the Belgian study involving bakery workers (n 246 from 74 bakeries) and a control group (n 251) recruited from a petrochemical plant there was no difference in sensitization to storage mites. They also found that 70 % of the storage mite sensitized also were sensitized to HDM, and concluded that storage mites should not be regarded as occupational allergens (Droste et al., 2003). It is questionable that they used a mean wheal diameter of only 2 mm as a positive response in the skin prick testing, and the overall sensitization rate is rather high. But this study nevertheless gives support to de Zotti and others that storage mites should be regarded foremost as common allergens (de Zotti et al., 1994).

On the other hand, Hytonen et al. (1997) found storage mites to be one of the most important causes to occupational rhinitis in general when using the Finnish Register of Occupational Rhinitis. This register has very strict inclusion criteria. Storage mite sensitization may be responsible for both rhinitis and asthma (Terho et al., 1985; Hytonen & Sala, 1996; Hage-Hamsten & Johansson, 1998). In the recently published study about laboratory animal workers with rhinoconjunctivitis Ruoppi et al. (2005) reported that sensitization to storage mites was common. They found that it was not a result of cross-reactivity to HDM, and concluded that the sensitization to storage mites might be work related. Since there are great differences in the numbers and types of mites found in different climactic regions, and some studies point to storage

mites, it is difficult to completely rule out the possibility that at least in some bakery workers the storage mites are the cause of occupational airway disease.

6.3.4 Occupational rhinitis and disability compensation

As presented in the introduction rhinitis may cause substantial morbidity, and rhinitis patients may suffer even more than those with moderate asthma in some aspects of QoL. If we make the assumption that OcR decreases the QoL more or less to the same extent as rhinitis, the possibility to apply for disability compensation as in OA should be granted. So far the legislation in most countries is lagging behind in this respect, and in most countries as in Norway, does not include OcR as possible ground for disability compensation. In Norway there are some few cases where a contracted rhinitis has been approved as caused by the occupation, and for the worker this results in free medical service, and medication. To be granted disability compensation the overall handicap has to be rated 15 % or more, and so far this author does not know of any such cases in Norway.

When trying to evaluate disability the most used terms are ‘impairment’, ‘disability’ and ‘handicap’ (Balkissoon, 2003). The definitions according to the World Health Organization (WHO) (1980) are:

Impairment: any loss or abnormality of psychological, physiological, or anatomical structure or function.

Disability: any restriction or lack of ability to perform any activity within the range of ‘normal’ for a human being.

Handicap: disadvantage resulting from an impairment/disability that limits/prevents fulfilment of that person’s normal role depending on sex, age, social, and cultural factors.

If one should try to outline guidelines for the evaluation of OcR we may look at existing guidelines for OA. ATS guidelines from 1993 give algorithms for the possible diagnosis of OA, and the process of impairment evaluation (Guidelines for

the evaluation of impairment/disability in patients with asthma, 1993). The rating of impairment is divided in 3 different features of OA with scoring in each feature, all based on objective measurements or controllable data; 1) postbronchodilator FEV1, 2) reversibility of FEV1, or degree of airway hyperresponsiveness, and 3) minimum medication need. The total score is used to place the individual case in impairment class from zero to five.

The literature is very sparse on this matter regarding OcR. Drake-Lee et al. (2002) in their review account for some of the difficulties encountered, and use the loss of smell as an example of possible impairment due to rhinitis. The loss of smell is not uncommon in bakery workers, and for some individuals of great impact on QoL. This possible handicap illustrates some of the problems with OcR in this context. It is difficult to assess objectively the degree of impairment, also because we do not know what is 'normal'. And the judgement has to rely on the physicians arbitrarily and subjective scaling. It would be easier to evaluate the impairment of nasal patency since we have more reliable methods, although we may have problems to assess the individuals' nasal patency prior to the occupational acquired impairment.

Considering the close link between rhinitis and asthma, the evidence of increased burden of morbidity if rhinitis is experienced together with asthma, and the aspects discussed above, we propose that OcR at least should be taken into account when evaluating the overall handicap in OA. This until we, based on future research, may put forward suggestions for insurance legislation for OcR as such, and may make guidelines for the evaluation of OcR disability.

6.4 Bronchial hyperresponsiveness

The pharmacological substances metacholine and histamine causes bronchoconstriction by a direct effect on the effector cells, predominantly the smooth muscle cells, but also on mucus glands and on airway microvasculature, and without involving intermediate pathways (Joos et al., 2003). In the late eighties the concept of

indirect bronchial challenges was developed (Pauwels et al., 1988). Indirect challenges act by causing the release of endogenous mediators that cause the airway smooth muscle to contract (Joos et al., 2003). Indirect bronchial provocations (exercise, adenosine, hyperventilation, non-isotonic aerosols as mannitol) reflect more directly the ongoing airway inflammation and are more specific, but less sensitive, to asthma (Joos et al, 2003).

In Paper III we found a lack of concordance between the BHR expression and IgE-sensitization. In part this may be attributed to the fact that the effect of metacholine on the bronchi is more related to the smooth muscles and bronchoconstriction, and thereby airway calibre, than to inflammation processes in the bronchial mucosa. Van den Berge et al. (2001) found PC_{20} to AMP more closely associated with eosinophilic airways inflammation than PC_{20} metacholine. In a review Joos (2003) conclude that bronchial responsiveness to a direct stimulus is only weakly related to airway inflammation.

Chinn and Schouten (2005) have recently reviewed the many papers where the bronchial challenge data are expressed as a continuous outcome. Most of these studies are based on provocation using a dosimeter method. We present a method for expressing bronchial challenge data as a continuous outcome after using a tidal breathing method with a Wright nebuliser. The ERS task force states that the direct provocation methods are less suitable for epidemiologic studies (Joos et al, 2003). Sterk (2002) in his review on airway responsiveness are concerned about their moderate specificity, and their relatively low negative predictive value for asthma, and also find them less useful in epidemiologic studies. However, in the same review he also emphasizes the great advantage of the direct methods since they express bronchial responsiveness that ‘positively distinguishes itself from cellular or molecular markers of inflammation’. He postulates that metacholine responsiveness may be particularly suitable in the long-term monitoring of asthma. Sont et al. (1999) found in a 2 year follow up of asthmatics that those where the treatment was guided also by PC_{20} to metacholine had a 50% reduction in cumulative incidence of

exacerbations as compared to the group following the reference treatment strategy. The main advantage of our expression of the metacholine data as a continuous outcome would be in a follow up of our bakery workers.

22 % of the bakery workers had a baseline FEV_1 less than 80 % of predicted. Unfortunately we have not post-dilator spirometry data, and therefore cannot relate these data to COPD-guidelines. As shown in Paper I the proportion of smokers in the bakery worker group is high (45.8%) and the risk of COPD development in this occupation should be accordingly considerable. Bronchial hyperresponsiveness to metacholine is present in a majority of smokers with mild to moderate COPD (Tashkin et al., 1992).

6.5 'Occupational United Airways'?

It is now recognized that allergic rhinitis and asthma are two clinical manifestations of a single disorder of the airways (Passalacqua & Canonica, 2000; Bousquet et al., 2001). This view is supported by numerous epidemiological, clinical and immunological observations.

Do these concepts apply to the occupationally acquired airway diseases? An important and often cited paper gives evidence for this concept (Karjalainen et al., 2003): 'Increased risk of asthma among workers with occupational rhinitis'. The paper is based on the Finnish Register of Occupational Diseases, a national register revealing data on asthma medication, and the Population Register Centre used to account for the vital status of each participant at the study's end point. Again, the diagnosis in focus is the *allergic* occupational rhinitis since the criteria for inclusion also had incorporated 'sensitization to a specific agent at work'. Anyway, it gives very strong support to the concept of the Occupational Allergic United Airways.

We found that the debut of nasal symptoms preceded lower airway symptoms. This is in line with previous studies (Hytonen et al., 1997; Baur, 1999; Malo et al., 1997).

But a recently published prospective study in a group of apprentice bakers questions this opinion (Walusiak et al., 2004). In this study they did not find any difference in the mean latent period until development of rhinitis and the first chest symptoms. Walusiak has made a comment on this in a review saying: 'A limitation of that study is that the data were based on participant recollection, so it is possible that the patients may not have noticed rhinitis symptoms early enough as they are less worrying than the chest symptoms' (Walusiak, 2006). The same objection may in part apply for our findings in the interviews presented in Paper I since they were also based on participant recollection. In the interview the participants were asked to report the year the nasal and chest symptoms started, and if uncertain were asked whether they experienced the upper or lower airway symptoms to appear first.

Casale and Dykewicz present an alternative viewpoint that allergic rhinitis, asthma, and atopic dermatitis are all manifestations of a systemic immunologic disorder that produces a variety of allergic diseases that affect different organ systems (Casale & Dykewicz, 2004). They claim that this hypothesis acknowledges both the apparent overlap and the differences between these conditions and points toward the development of new therapies targeting the underlying systemic cause. The weight is on the term 'systemic'. This is in contrast to the 'United Airways' theory of allergic rhinitis and asthma as two clinical manifestations of a single disorder confined to the respiratory tract.

We agree with Passalacqua et al. in the ending remark of their review (2000): 'Obviously, some questions remain unanswered: in particular, the relative weight and role of allergy as compared with other possible mechanisms that are involved, for instance, in non-atopic subjects'. Our data showed that probably also the non-IgE mediated OcR causes inflammation in the mucosa (higher levels of α_2-macroglobulin), exhibits exudative hyperresponsiveness, and surprisingly, also reveals increased level of mucosal ECP, otherwise been thought of as a feature especially of IgE mediated conditions. Although the groups became too small for meaningful statistical analyses, the tendency was quite clear; the levels of indices of

inflammation were as high (or even sometimes higher) in those with no atopy and in those without any occupational sensitization when looking at the workers with nasal symptoms or a diagnosis of occupational rhinitis.

Our study (Paper I) found an association between the non-IgE-mediated OcR categories and the questionnaire derived asthma symptom complex, highest effect for non-IgE-mediated OcR-I. Accordingly, it seems important to recognize individuals with non-IgE-mediated OcR and to consider them to be at risk of contracting lower airway symptoms and asthma, as we do with individuals with IgE-mediated OcR.

6.6 The national exposure limit of flour dust: time for revision?

The present exposure limit for flour dust in Norway is 3 mg/m^3 (inhalable). Mean exposure to flour dust was below this limit in 3 of the bakeries, but all 6 bakeries included in our study had measurements above this limit in the dough-making area.

We have used the Gelman standard cassette, measuring what has been called total dust. Kruse et al. (2004) have compared 3 filter holders; GSP, IOM, STK (standard cassette, same as our Gelman) with the PAS6 as reference. They found that the STK underestimated, and the GSP and IOM overestimated the amount of flour dust measured in 2 bakeries, one small and one large bakery. The correlation between STK and PAS6 was very good, with $R^2 = 0.90$, and the precision better when compared to IOM and GSP (significantly lower SD). They concluded that the STK measurements should be adjusted with a factor of 1.75 to be comparable to measurements by GSP and PAS6. If we do so the exposure limit is clearly exceeded in all bakeries studied.

The Dutch group in Wageningen presented in 1998 a further analysis of the data from their epidemiological survey in a group of bakery workers. They concluded that the work related sensitization risk will be negligible if exposure levels are reduced to average exposure concentration of approximately 0.5 mg/m^3 inhalable dust during a

work shift (Houba et al., 1998a). Our data give support to the hypothesis of a dose-response relationship between current exposure level of flour dust and both upper respiratory symptoms and indices of nasal inflammation. We were able to show a significant difference between high and low levels of symptoms/indices of inflammation above and below an exposure level of 1 mg/m^3 total dust. If we follow the recommendation from Kruse et al. (2004) this exposure level may be calculated to be the equal of 1.75 mg/m^3 inhalable.

Ideally the exposure limit of flour dust should be as low as 0.5 mg/m^3 inhalable. In view of the great costs for many bakeries to implement the necessary changes to accommodate this exposure limit the limit may be set to 2 mg/m^3 inhalable as a first step, but with a predetermined condition that the exposure limit should be further lowered to 1 mg/m^3 in 5-7 years.

7. Conclusions

Different criteria for the diagnosis of OcR, especially whether claiming one or two of the main nasal symptoms, result in considerable dispersion of the prevalence estimates. There is a need for a consensus on the criteria of OcR.

OcR is related to asthma symptoms regardless of occupational sensitization or not.

Storage mites may be important occupational allergens in Norwegian bakeries. Nearly one third of the bakery workers (30%) are sensitized to an occupational allergen.

The occupational rhinitis is characterized by eosinophilic, exudative inflammation and exudative hyperresponsiveness. This is not dependent on IgE-sensitization.

The mean workplace dust exposure level is above the national exposure limit of 3 mg/m^3 inhalable in the dough-making area.

There is a dose-response relationship between workplace dust exposure level and airway symptoms, and between workplace dust exposure level and indices of nasal inflammation. There is not a clear relationship between workplace dust exposure level and IgE-sensitization or bronchial responsiveness.

Bronchial responsiveness measured after metacholine challenge using a tidal breathing method is related to baseline lung function, smoking, lower airway symptoms and elevated levels of ECP in the nasal mucosa. The $slope_{conc}$ expression seems useful in revealing the results of bronchial metacholine provocation as a continuous outcome.

A possible relationship between upper and lower airway disease in the bakery workers is supported by finding OcR strongly related to asthma symptoms, the work related nasal symptoms emerging before lower airway symptoms, and that nasal ECP as a marker of eosinophil activation is found in higher amounts in those with bronchial hyperresponsiveness.

8. Future directions of research and prophylaxis

8.1 Assessing the nasal inflammation in the individual

In the before-mentioned ATS/ERS report from Tarlo & Malo (2006) they state that functional and inflammatory tests of the nose are not as standardised as those aimed at assessing the lower airways. One of their 100 key questions is therefore: 'How can the methodology of nasal challenges and understanding of relationships with OA be improved?'

Is it possible to develop the nasal lavage method to an individual diagnostic tool, with normality values defining active inflammation or not, and made feasible to be used in an occupational setting? As discussed above may the histamine challenge test with indices of inflammation measured in nasal lavage as the outcome be a valuable inflammatory test in the nose. This methodology should be scrutinized, and it should be clarified whether it may serve as a test of the individual.

The histamine challenge test could be combined with Nasal Peak Inspiratory Flow, or another measurement of nasal patency as Nasal Peak Expiratory Flow or Acoustic Rhinometry (Anterior Rhinomanometry being too laborious in clinical practice). Again, it is not clarified whether this could serve as a test of the individual on inflammation (Castano & Thierault, 2006). Nasal NO as an individual diagnostic tool to assess nasal inflammation should be explored as well.

8.2 Non-IgE mediated OcR

Non-IgE mediated occupational rhinitis should be recognized. We lack a characterization of this entity, and the causative mechanisms should be elucidated. It is especially important to find out whether the non-IgE mediated OcR is a risk factor for asthma development as well as IgE mediated rhinitis (Karjalainen et al., 2003).

8.3 QoL in occupational airway disease

There are few, if any, studies on OcR's and OA's effect on quality of life. The question whether new instruments for measuring QoL in the occupational setting have to be developed needs attention.

8.4 Questionnaire validation

Which rhinitis questions may serve as good markers of work relation? Is it possible to formulate rhinitis questions that single out those with inflammation in the nasal mucosa? The need for a validation of a questionnaire on OcR is also mentioned in a review by Siracusa (2000).

8.5 Miscellaneous

The occupational setting may be ideal as a model-system for elucidating the process of sensitization, and future studies in bakeries or other occupational settings may further advance our understanding of the link between upper and lower airways.

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10. Errata

Paper I:

Instead of ‘Forty-one of the workers (23%)’ should be ‘Sixty-one of the workers (34%)’ (p.1213, beginning of 4th passage).

Instead of ‘Seventy-six (42%)’ should be ‘Seventy-seven (43%)’ (p.1213, 4th passage).

In reference number 17: Should be ‘1989’ instead of ‘1998’, and author name (Dreborg S) should be omitted (p. 1217).

Paper II:

In the Method chapter the mould *Clad. Herbarium* should be categorized as an occupational allergen, instead of a common aeroallergen (p. 24, 4th passage).

Instead of ‘Walusiak J, Wiszniewska M, Krawczyk-Adamus P, Palczynski C. Occupational allergy to wheat flour. Nasal response to specific inhalative challenge in asthma and rhinitis vs. isolated rhinitis: a comparative study. *Int J Occup Med Environ Health* (2004); **17**: 433-440’ as the last reference there should be: ‘Walusiak J, Hanke W, Gorski P, Palczynski C. Respiratory allergy in apprentice bakers: do occupational allergies follow the allergic march? *Allergy* 2004; **59**:442-450’ (In the references: p. 29).

11. Appendix

Table 1-appendix: The 235 dust measurements using the Gelman sampling device dispersed between the different work tasks and bakeries:

Bakery	Work task	Number of meas-urements	Aritmetic mean [mg/m^3]	Lowest value [mg/m^3]	Highest value [mg/m^3]
A	Dough-making Day	3	6,13	3,97	8,19
	Dough-making Night	8	1,93	0,93	3,48
B	Dough-making/Weighing	2	12,95	11,40	14,50
	Dough-making/Bread-forming	7	4,65	2,27	6,59
	Dough-making Night	3	4,23	3,12	6,03
C	Dough-making	11	5,82	1,08	16,56
D	Dough-making	10	2,57	1,57	3,96
E	Dough-making	12	2,89	2,09	4,16
F	Dough-making	5	2,53	1,14	4,77
F	Dough-making/Extruder	5	2,36	1,91	3,44
A	Bread-forming	4	4,42	0,95	9,15
B	Bread-forming	19	1,46	0,68	3,06
C	Bread-forming	5	1,37	0,64	1,97
D	Bread-forming	12	1,63	0,26	4,77
E	Bread-forming	7	1,80	1,22	2,52
A	Confectionary	4	0,67	0,55	0,80
B	Confectionary	4	1,72	0,41	3,25
C	Confectionary	Not meas.			
D	Confectionary	Have not			
E	Confectionary	11	2,45	0,58	5,35
F	Confectionary	Have not			

A	Oven workers	4	0,86	0,33	1,87
B	Oven workers	9	0,31	0,17	0,46
C	Oven workers	5	1,03	0,50	1,54
D	Oven workers	1	0,65		
E	Oven workers	Not meas.			
F	Oven workers/Stationary	5	0,73	0,69	0,77
A	Packing	8	0,09	0,02	0,16
B	Packing	8	0,35	0,06	0,84
C	Pakking Day	5	0,25	0,21	0,31
	Pakking Night	2	0,51	0,50	0,52
D	Packing	10	0,43	0,19	1,81
E	Packing	6	0,39	0,31	0,47
F	Packing	10	0,45	0,27	0,72
	Packing. Stationary. ‘Tørrlefse’	5	0,44	0,24	1,00
	Packing Stationary Cinnamon	5	0,52	0,26	0,72
A	Administration	5	0,03	0	0,05
B	Administration Stationary	4	0,05	0,01	0,07
C	Adm./Lunch-room/Stationary	2	0	0	0
D	Administration	Not meas.			
E	Shop. Stationary	3	0,14	0	0,26
F	Administration	Not meas.			
A	Cleaning (whole bakery)	6	0,17	0,08	0,23
	211 (Personal) + 24 (Stationary)	235			

Table 2-appendix: English version of the questionnaire:

Investigation of employees in bakeries and in other occupations

Thank your for participation in the investigation of employees in the bakeries and in other occupations here in Bergen County. There has not previously been undertaken such an investigation in Norway. All information will be treated confidentially. The investigation has been approved by the Regional National Committee for Research Ethics and the Norwegian Data Inspectorate.

Most of the questions are yes/no questions, and almost all questions are meant to be answered by ticking in the most appropriate box. Several of the questions may seem nearly identical, but you should answer them all.

Important! For those who have answered a similar questionnaire before it is important to convey that we do not ask you to answer once again in order to test you, but to test the questionnaire!

1.	Surname:	Forename:

		Day		Month		Year	
2.	Date of birth						
3.	Date of attendance:						

4. Gender: Woman ☐ Male ☐

Airway symptoms

5. Have you ever the last 12 months experienced wheezing? Yes ☐ No ☐

If 'no', proceed to question 8

6. Have you been dyspnoeic when wheezing? Yes ☐ No ☐

7. Have you experienced wheezing when not having a cold? Yes ☐ No ☐

8. Have you ever the last 12 months woke up in the morning with chest tightness? Yes ☐ No ☐

9. Have you ever the last 12 months woke up in the middle of the night with attacks of chest tightness?

Yes ☐ No ☐

10. Have you ever the last 12 months woke up with coughing attacks? Yes ☐ No ☐

11. Have you in the last 12 months had asthma attacks? Yes ☐ No ☐

12. Do you at present use asthma medication? (Included inhalators and tablets) Yes ☐ No ☐

13. Have you ever when not having a cold or the flu had nose problems as:

a) Sneezing or itching? Yes ☐ No ☐

b) A running nose? Yes ☐ No ☐

c) Nose blockage? Yes ☐ No ☐

14. Have you had such nose problems in the last 12 months? Yes ☐ No ☐

15. **If Yes on question 14:**

When did you experience the nose problems? (You may tick several times)

☐ Spring ☐ Summer ☐ Autumn ☐ Winter

16. Did you at the same time when you had the nose problems experience itching or running eyes? Yes ☐ No ☐

17. Did the nose problems get worse when you came in contact with:

☐ pollen (trees/flowers/grass)? ☐ house dust? ☐ flour?

☐ other types of dust? ☐ cat/dog/horse/other animals?

(You may tick several boxes)

18. Have you ever had hay fever? Yes☐No☐Don't know☐

19. Have you ever had children's eczema/atopic dermatitis? Yes☐No☐Don't know☐

20. Do you regularly cough or clear your throat in the morning? Yes ☐ No ☐

21. Do you cough daily for 3 months or more in one year? Yes ☐ No ☐

22. Do you become dyspnoeic when walking two stairs at normal speed? Yes ☐ No ☐

23. Have you ever experienced wheezing? Yes ☐ No ☐

24. Have you ever been treated by a physician or in a hospital for the following diseases:

a. Asthma — Yes ☐ No ☐

b. Bronchitis — Yes ☐ No ☐

25. Have any of these biologic relatives of you had asthma?

Mother: Yes☐No☐Don't know☐

Father: Yes☐No☐Don't know☐

26. How many brothers and sisters have do you have/have you had? Number: ☐

27. How many of your brothers and sisters have had asthma? Number: ☐

28. Have you previously tested positive on allergy tests? Yes ☐ No ☐

29. Have any of these biologic relatives of you had allergy:

Mother: Yes☐No☐Don't know☐

Father: Yes☐No☐Don't know☐

30. How many of your brothers and sisters have had allergy? Number: ☐

31. Have you been using allergy medication or medication for the nose or the lungs the last year? Yes ☐ No ☐

32. Do you have knowledge about any employee at your working place that had to quit the job because of work related health problems from the eyes, skin, nose or the lungs? Yes ☐ No ☐

Work related symptoms:

When did you experience the health problems? (If you still experience the health problem do not fill in the last year)

33. Have you had work related nasal symptoms when not having a cold or the flu? Yes ☐ No ☐ 20 . . – 20 . .

(If 'no', proceed to question 38)

34. Which of these nasal symptoms have you experienced when at work? (You may check out more than one)

a. Nose running ? Yes ☐ No ☐

b. Itching ? Yes ☐ No ☐

c. Sneezing ? Yes ☐ No ☐

d. Nose blockage ? Yes ☐ No ☐

35. Do the nasal symptoms trigger of or worsen when you come in contact with: ☐ Flour? ☐ Baking additives? ☐ Cinnamon?

☐ Other baking ingredients? Which?. . . . . .

36. Do your nasal symptoms improve in the weekends/vacations? Yes ☐ No ☐

37. How often do you experience nasal symptoms at work?
Occasionally ☐ Weekly ☐ Daily ☐

			When did you experience the health problems? (If you still experience the health problem do not fill in the last year)
38.	Have you or have you had work related eye symptoms?	Yes ☐ No ☐	20 . . – 20 . .
39.	Do your eye symptoms improve during weekends/vacations?	Yes ☐ No ☐	
40.	Have you or have you had work related hand eczema?	Yes ☐ No ☐	20 . . – 20 . .
41.	Does your hand eczema improve in weekends/vacations?	Yes ☐ No ☐	
42.	Have you ever experienced wheezing when at work?	Yes ☐ No ☐	20 . . – 20 . .
43.	Have you ever experienced chest tightness at work?	Yes ☐ No ☐	20 . . – 20 . .
44.	Have you ever experienced wheezing and chest tightness at the same time when at work?	Yes ☐ No ☐	
45.	Have you occasionally experienced wheezing and chest tightness in the evening or at night after work?	Yes ☐ No ☐	20 . . – 20 . .
46.	Have you experienced coughing at work?	Yes ☐ No ☐	20 . . – 20 . .
47.	Have you experienced coughing after work?	Yes ☐ No ☐	20 . . – 20 . .
48.	Do you improve from these symptoms (questions 47-52) in weekends/vacations?	Yes ☐ No ☐	

49. Do you wheeze during or after physical activities when not at work? Yes ☐ No ☐

50. Do you wheeze during or after physical activities at work? Yes ☐ No ☐

Information on smoking

51. Do you smoke or have you ever smoked more than 1 cigarette daily for one year?

☐ Yes, daily smoker

☐ Yes, but quitted smoking *less* than one year ago

☐ Yes, but quitted smoking *more* than one year ago

☐ No, never smoker

Thank you for your participation!

Table 3-appendix: Norwegian version of the questionnaire:

UNDERSØKELSE AV BAKERIANSATTE OG ANDRE YRKESAKTIVE

Takk for at du vil være med i undersøkelsen av bakeriansatte og andre yrkesaktive i Bergen og omegn. Det er ikke tidligere gjort en slik undersøkelse i Norge. Alle opplysningene vil bli behandlet strengt konfidensielt. Undersøkelsen er godkjent av den regionale Etiske Komite og Datatilsynet.

De fleste spørsmålene er ja/nei-spørsmål, og nesten alle spørsmålene skal besvares med å krysse av i den eller de firkantene som passer best. Flere av spørsmålene kan virke veldig like, men svar på alle likevel.

Viktig! Til de av dere som har svart på et lignende spørreskjema tidligere er det viktig å si at vi ber deg ikke om å svare en gang til for å sjekke deg, men for å sjekke spørreskjemaet!

1. Etternavn: | Fornavn:

	Dag		Mnd		År	
2. Fødselsdato						
3. Utfylt dato:						

4. Kjønn: Kvinne ☐ Mann ☐

Luftveisplager

5. Har du noen gang i løpet av de siste 12 månedene hatt pipelyder (piping) i brystet ? (Med pipelyder menes høye eller dype lyder som også kan være svake) Ja ☐ Nei ☐

Hvis «nei», gå til spørsmål 8

6. Har du vært tungpusten i forbindelse med at du hadde pipelyder i brystet? Ja ☐ Nei ☐

7. Har du hatt slike pipelyder når du ikke har vært forkjølet ? Ja ☐ Nei ☐

8. Har du noen gang i løpet av de siste 12 månedene våknet om morgenen med følelse av å være tung i pusten? Ja ☐ Nei ☐

9. Har du noen gang i løpet av de siste 12 månedene våknet i løpet av natten med anfall med tung pust? Ja ☐ Nei ☐

10. Har du noen gang i løpet av de siste 12 månedene våknet med anfall av hoste ? Ja ☐ Nei ☐

11. Har du i løpet av de siste 12 månedene hatt astma-anfall ? Ja ☐ Nei ☐

12. Bruker du astma-medisiner nå? (Inkludert spray pulverinhalasjon eller tabletter) Ja ☐ Nei ☐

13. Har du noen gang når du ikke var forkjølt eller hadde influensa hatt neseplager i form av:

a) Nysing eller kløe? Ja ☐ Nei ☐

b) Neserenning? Ja ☐ Nei ☐

c) Nesetetthet? Ja ☐ Nei ☐

14. Har du hatt slike neseplager siste 12 måneder? Ja ☐ Nei ☐

15. **Hvis ja på spørsmål 14:**

Når hadde du neseplagene? (Du kan sette kryss flere steder)

☐ Vår ☐ Sommer ☐ Høst ☐ Vinter

16. Hadde du samtidig med neseplagene kløende eller rennende øyne? Ja ☐ Nei ☐

17. Ble neseplagene verre når du kom i kontakt med:

☐ pollen (trær/blomster/gress)? ☐ husstøv? ☐ melstøv?

☐ annet støv? ☐ katt/hund /hest/andre dyr?

(Sett gjerne flere kryss)

18. Har du noen gang hatt høysnue? Ja ☐ Nei ☐ Vet ikke ☐

19. Har du noen gang hatt barneeksem (atopisk dermatitt = kløende eksem i albuebøyninger/knehaser/ansikt)? Ja ☐ Nei ☐ Vet ikke ☐

20. Hoster eller harker (kremter) du vanligvis om morgenen? Ja ☐ Nei ☐

21. Hoster du daglig tilsammen 3 måneder eller lenger i løpet av ett år? Ja ☐ Nei ☐

22. Blir du tungpusten når du går opp 2 etasjer i vanlig fart? Ja ☐ Nei ☐

23. Har du noen gang hatt piping (pipelyd) i brystet? Ja ☐ Nei ☐

24. Har du noen gang vært behandlet av lege eller vært innlagt i sykehus for disse sykdommene:

a. Astma Ja ☐ Nei ☐

b. Bronkitt Ja ☐ Nei ☐

25. Har følgende av dine biologiske slektninger hatt astma?

Mor: Ja ☐ Nei ☐ Vet ikke ☐

Far: Ja ☐ Nei ☐ Vet ikke ☐

26. Hvor mange søsken har/hadde du? Antall: ☐

27. Hvor mange av dine søsken har/hadde astma? Antall: ☐

28. Har du tidligere testet positivt på allergiprøver? Ja ☐ Nei ☐

29. Har følgende av dine biologiske slektninger hatt allergi?

Mor: Ja ☐ Nei ☐ Vet ikke ☐

Far: Ja ☐ Nei ☐ Vet ikke ☐

30. Hvor mange av dine søsken har hatt allergi? Antall: ☐

31. Har du brukt allergimedisiner eller medisiner for nesen eller lungene det siste året? Ja ☐ Nei ☐

32. Kjenner du til at noen på din arbeidsplass har sluttet i jobben på grunn av plager de fikk i arbeidet fra øyne, hud, nese eller lunger? Ja ☐ Nei ☐

Symptomer i forbindelse med arbeidet:

Når hadde du plagene? (Hvis du fremdeles er plaget, setter du siste årstall åpent)

33. Har du hatt plager fra nesen når du er på jobb og ikke er forkjølt eller har influensa? Ja ☐ Nei ☐ 19 . . – 19 . .

(Hvis "nei", gå til spørsmål 38)

34. Hvilke av disse neseplagene har du hatt på jobb: (Du kan krysse av for flere)

a. Renning fra nesen ? Ja ☐ Nei ☐

b. Kløe ? Ja ☐ Nei ☐

c. Nysing ? Ja ☐ Nei ☐

d. Nesetetthet? Ja ☐ Nei ☐

35. Utløses eller forverres neseplagene når du kommer i kontakt med:
☐ Melstøv? ☐ Bakehjelpemidler? ☐ Kanel?

☐ Andre bakeringredienser? Hvilke: . . . . . .?

36. Blir du bedre av neseplagene i friperioder (helger,ferier)? Ja ☐ Nei ☐

37. Hvor ofte har du neseplager når du er på jobb?
Av og til ☐ Ukentlig ☐ Daglig☐

			Når hadde du plagene?
38.	Har du eller har du hatt plager fra øynene når du er på jobb?	Ja ☐ Nei ☐	19 . . – 19 . . (Hvis du fremdeles er plaget, setter du siste årstall åpent)
39.	Blir du bedre av plagene fra øynene i friperioder (helger,ferier)?	Ja ☐ Nei ☐	
40.	Har du eller har du hatt håndeksem når du er på jobb?	Ja ☐ Nei ☐	19 . . – 19 . .
41.	Blir du bedre av håndeksemet i friperioder (helger,ferier)?	Ja ☐ Nei ☐	
42.	Har du noen gang fått pipelyder i brystet på jobb?	Ja ☐ Nei ☐	19 . . – 19 . .
43.	Har du noen gang blitt tungpusten på jobb?	Ja ☐ Nei ☐	19 . . – 19 . .
44.	Har du hatt piping i brystet og vært tungpusten på samme tid når du har vært på jobb?	Ja ☐ Nei ☐	

45.	Har du av og til hatt piping og vært tungpusten om kvelden eller natten etter jobb ?	Ja ☐ Nei ☐	19 . . – 19 . .
46.	Har du vært plaget av hoste på jobb?	Ja ☐ Nei ☐	19 . . – 19 . .
47.	Har du vært plaget av hoste etter jobb?	Ja ☐ Nei ☐	19 . . – 19 . .
48.	Blir du bedre av disse plagene (spm 47-52) i friperioder (helger,ferier)?	Ja ☐ Nei ☐	
49.	Får du piping i brystet under eller etter anstrengelser i fritiden?	Ja ☐ Nei ☐	
50.	Får du piping i brystet under eller etter anstrengelser på jobben?	Ja ☐ Nei ☐	

Røykeopplysninger

51. Røyker du eller har du røykt noen gang mer enn svarende til 1 sigarett daglig i ett år ?

☐ Ja, røyker

☐ Ja, men sluttet å røyke for *mindre* enn ett år siden

☐ Ja, men sluttet å røyke for *mer* enn ett år siden

☐ Nei, aldri røykt

TAKK FOR INNSATSEN !

Table 4-appendix: English version of work task scheme:

Bakery and duration of employment:

Write the name of all bakeries you have worked in, and when you were employed. Start with the last, and go backward in time.

Bakery:	Duration of employment:	Work tasks:
……	from 19…….. - until today	D U O P K L R A
……	from 19…….. - 19……	D U O P K L R A
……	from 19…….. - 19……	D U O P K L R A
……	from 19…….. - 19……	D U O P K L R A
……	from 19…….. - 19……	D U O P K L R A
……	from 19…….. - 19……	D U O P K L R A

Work tasks:

1. Mark with a cross (X) your most common work task in each bakery.

2. Mark with a circle (O) all other work tasks that you do more than one hour each day.

Example:D U ~~O~~ P K L (R) A (The most common work task is oven work, but do also cleaning more than one hour every day)

D = Doughmaking

U = Breadforming

O = Oven work

P = Packing/Transport

K = Pastry

L = Supervisor

R = Cleaning

A = Other tasks/Office staff

Table 5-appendix: Norwegian version of work task scheme:

BAKERI OG ANSETTELSESTID:

Skriv navn på samtlige bakerier du har arbeidet i, og når du var ansatt. Start med det siste, og gå bakover i tid.

Bakeri:	Ansettelsestid:
……	fra 19…….. - til i dag
……	fra 19…….. - 19……
……	fra 19…….. - 19……
……	fra 19…….. - 19……
……	fra 19…….. - 19……
……	fra 19…….. - 19……
……	fra 19…….. - 19……
……	fra 19…….. - 19……

ARBEIDSOPPGAVER:

1. Marker med kryss (X) din vanligste arbeidsoppgave i hvert bakeri.

2. Marker med runding (O) de andre arbeidsoppgavene dine som hver for seg utgjør minst 1 times arbeid per dag.

Eksempel: D U ~~O~~ P K L (R) A (Vanligste oppgave er ovnspassing, men gjør også rengjøringsarbeid i tilsammen 1 time eller mer hver dag)

D U O P K L R A

D U O P K L R A

D U O P K L R A

D U O P K L R A

D U O P K L R A

D U O P K L R A

D U O P K L R A

D U O P K L R A

D = Deigblanding/Elting

U = Utbaking/Oppslåing/Linjearbeid

O = Ovnspassing/Steking

P = Pakking/Transport

K = Konditorarbeid

L = Arbeidsledelse

R = Rengjøring

A = Andre oppgaver/Kontor

Paper I

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ORIGINAL ARTICLE

Occupational rhinitis: diagnostic criteria, relation to lower airway symptoms and IgE sensitization in bakery workers

TORGEIR STORAAS[1], SVERRE KARMHUS STEINSVÅG[1], ERIK FLORVAAG[2], ÅGOT IRGENS[3] & TOR BRØVIG AASEN[3]

[1]*Department of Otolaryngology, Head & Neck Surgery,* [2]*Laboratory of Clinical Biochemistry and* [3]*Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway*

Abstract

Conclusions. The use of different diagnostic criteria has considerable consequences for the prevalence estimates of occupational rhinitis. There is a strong relationship between occupational rhinitis and lower airway symptoms. Storage mites appear to be important occupational allergens in Norwegian bakeries. *Objectives*. To study the consequences of various diagnostic criteria on the prevalence of occupational rhinitis, assess the prevalence of IgE sensitization and explore the relationships between upper and lower airway symptoms and between symptoms and IgE sensitization. *Material and methods*. A total of 197 employees in 6 bakeries were interviewed and completed a questionnaire. A skin prick test was performed, total and specific IgE were determined and a histamine release test was performed for relevant allergens. The criteria for the diagnosis of occupational rhinitis were based on the 1994 International Consensus Report on Rhinitis. *Results*. The prevalence of occupational rhinitis varied between 23% and 50%, depending on the criteria used. The occurrence of nasal symptoms was found to precede the development of lower airway symptoms. Occupational rhinitis, both IgE- and non-IgE-mediated, was associated with asthma symptoms. The most frequent causes of sensitization (20%) were different species of storage mites. Storage mite sensitization was related to occupational rhinitis and work exposure.

Keywords: *Asthma, flour, International Consensus Report on Rhinitis, storage mites*

Introduction

Many authors have reported high prevalences of occupational rhinitis in bakeries [1,2]. However, there seems to be no consensus in the literature regarding the diagnostic criteria. The definitions range from "any rhinitic symptom reported as work-related, excluding malignant diseases" [3] to the strictest criteria expressed in the International Consensus Report of 1994 [4]. There seems to be an increased risk of asthma among workers with occupational rhinitis [5] and nasal symptoms usually precede the occurrence of lower airway symptoms [6–8]. However, these views were questioned in a recently published prospective study [9]. In 1929, De Besche [10] introduced the idea of baker's asthma as an allergic occupational disease, but non-allergic reactions are also involved in both baker's asthma and rhinitis [11].

In 1999 the cross-sectional study "Diagnosis and prevention of airborne allergy in bakers" was started in Bergen, Norway. The preliminary study revealed a high prevalence of symptomatic bakers (>50%), who mainly suffered from nasal symptoms. Most of them were not sensitized to either wheat or α-amylase [12]. The aims of the present investigation were to study the impact of various diagnostic criteria on the estimated prevalence of occupational rhinitis and to assess the prevalence of IgE sensitization. We also wanted to explore the relationships between upper and lower airway symptoms and between airway symptoms and IgE sensitization.

Material and methods

The study comprised all 197 employees in 6 bakeries (Table I). The number of employees in each bakery

Correspondence: Torgeir Storaas, MD, Department of Otolaryngology, Head & Neck Surgery, Haukeland University Hospital, N-5021 Bergen, Norway. Fax: +47 55 97 26 43. E-mail: torgeir.storaas@helse-bergen.no

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Table I. Demographic data for the 183 bakery workers.

Age (years)	
Mean	38
Range	16–66
SD	12
Length of service (years)	
Median	10
Range	1–44
Interquartile range	4–19
Gender; *n* (%)	
Male	125 (68.3)
Female	58 (31.7)
Smoking status; *n* (%)	
Daily smokers	83 (45.8)
Given up in last year	15 (8.3)
Given up >1 year ago	19 (10.5)
Non-smokers	64 (35.4)

varied between 14 and 84 (median 22). A total of 180 subjects (91%) completed a questionnaire, and 181 (92%) were interviewed. Serum samples for determination of total and specific IgE and heparinized blood for a histamine release test were obtained from 183 individuals (93%). A skin prick test was performed in 183 subjects (93%) fourteen workers did not want to attend. Based on the results of the questionnaires, the employees were grouped into production workers (dough-makers, bread-formers, packers, pastry-makers and drivers) and administrative staff.

Interview

A standardized interview was carried out by an otolaryngologist, and included questions about previous diseases, allergies, medication, smoking habits and work-related symptoms. The participants were asked to specify when each symptom appeared. The interviewer was blinded regarding the results of the questionnaires and tests.

The diagnostic criteria for occupational rhinitis (OcR) were based on the 1994 International Consensus Report (ICR) on the Diagnosis and Management of Rhinitis [4], in which rhinitis is defined as "Two or more nose symptoms (nasal discharge, blockage or sneeze/itch) for >1 h on most days" and OcR as "Rhinitis caused by exposure to an agent in the workplace". The work relationship was characterized by at least one of the following: an occupational trigger factor; improvement during vacations/weekends; and no history of nose problems before the start of employment. We defined four categories of OcR (Table II).

Each category of OcR was further divided into IgE-mediated and non-IgE-mediated based on documentation of sensitization to one or more of the occupational allergens [13].

Questionnaire

A self-administered questionnaire provided information on family history, general and work-related symptoms, work history and smoking habits as well as previous signs of allergy and atopic eczema/dermatitis syndrome. Questions regarding nose symptoms were mostly adopted from the International study of asthma and allergies in childhood (ISAAC) questionnaire [14]. Questions on triggering factors, improvement during vacations/weekends and the frequency of nose symptoms experienced at work were added.

The questionnaire-derived criteria for OcR-QI were two or more of the three previously defined rhinitis symptoms and work-related symptoms based on either the presence of a known trigger factor or improvement during vacations/weekends. In the data analysis we also included a category OcR-QII, for which only one of three work-related rhinitis symptoms had to be present.

The questions relating to asthma were taken from the Norwegian version of the European Community Respiratory Health Survey (ECRHS) [15,16]. "Asthma symptom complex" was defined as wheezing with breathlessness when not having a cold [16]. More specific work-related lower airway symptoms were also assessed, and we defined "work-related asthma symptom complex" as wheezing with breathlessness at work without having a cold.

Documentation of IgE sensitization

Occupational sensitization was defined as a positive test to one of the following allergens: wheat; α-amylase; oats; barley; rye; soybean; storage mites (Acarus siro, Lepidoglyphus destructor, Tyrophagus putrescentiae); the mold Cladosporium herbarium; or the cockroach Blatella germanica.

Serum IgE

Total and specific IgE were measured using the CAP-FEIA system (Pharmacia Diagnostics AB, Uppsala, Sweden). IgE specificities included the occupational allergen panel stated above. In addition, IgE towards common airborne allergens in Norway (the dust mite Dermatophagoides pteronyssinus, cat, dog, timothy and birch) was also assayed.

Skin prick test

Skin prick tests (SPTs) were performed according to the guidelines of the European Academy of

Table II. Categorization of OcR according to different diagnostic criteria.

Category	2 of 3 nose symptoms	1 of 3 nose symptoms	Duration >1 h/day most days	Relation to work
OcR-I	Yes		Yes	Yes
OcR-II		Yes	Yes	Yes
OcR-III	Yes			Yes
OcR-IV		Yes		Yes

Allergology and Clinical Immunology [17]. The applied technique gave a mean histamine weal diameter of 5.36 mm, and the coefficient of variation between histamine duplicates was 0.20 in 30 randomly chosen study participants. Soluprick® extracts (ALK-Abello, Hørsholm, Denmark) were used with the exception of α-amylase, where a 5% solution of Aspergillus oryzae (Sigma Chemical Co., St. Louis, MO) in saline was prepared.

Histamine release test

Histamine release from washed blood cells was studied using a glass fiber microtiterplate-based method, and the same allergen panel as used for the SPT [18].

Statistical methods

Statistical analyses were performed using SPSS 10.0 for Windows NT 4.0 (SPSS, Chicago, IL). ORs and corresponding 95% CIs were calculated. Analysis of relationships between symptoms, clinical signs, test results and the results of the questionnaires and interviews was performed with both crude ORs and multiple logistic regression adjusting for the potential confounders of age (or length of service), gender and smoking habits. Unless otherwise stated, the results of the logistic regression analysis are presented. With sparse numbers in some of the cells, an exact method (StatXact) was used to calculate the CI for the crude OR.

Those bakers who reported symptoms in the interview were asked to state the order of appearance of symptoms (nose, eyes, skin, lower airways). Assuming that each of these symptoms occurs randomly, we would expect that the probability of a symptom occurring first would be 0.25. Assuming this "first-symptom" null hypothesis to be true, we calculated the probability (p-value) of obtaining the observed number of employees with a specific symptom as the first from the binomial probability function. Workers who reported the first two symptoms simultaneously were excluded from the analysis.

The occurrence of a symptom among the first two reported, assuming an expected probability of 0.50, was calculated as above.

Ethical considerations

The Regional National Committee for Research Ethics (approval No. 282/98-83.98) and the Norwegian Data Inspectorate approved the study. Informed written consent was obtained from all participants prior to inclusion.

Results

Interview

The occurrence of nasal symptoms was found to precede the development of lower airway symptoms. Thirty of 61 workers (49%) reported a nose problem as the first symptom ($p < 0.001$), and 64/86 workers (74%) reported a nose symptom as 1 of the first 2 symptoms ($p < 0.001$). This was a higher frequency of preceding nose problems than would be expected at random.

The effects of applying different criteria for the diagnosis of OcR on the prevalences are shown in Table III. We found an association between the asthma symptom complex, both the ECRHS-derived and the more specific work-related complex, and all categories of OcR (Table III).

Questionnaire

Forty-one of the workers (23%) reported 2/3 rhinitis symptoms at work and either a specific baking ingredient that worsened the symptoms and/or an improvement during vacations/weekends. Seventy-six (42%) had 1 of 3 rhinitis symptoms related to work. Both Rhinitis categories (OcR-QI/QII) were associated with the asthma symptom complex, both the ECRHS-derived and the work-related complex (Table III).

The crude prevalences of the asthma symptoms (ECRHS questions) were higher than those reported from a random population in the ECRHS study in Bergen in 1991, as shown in Table IV [16].

A relationship with work was prevalent for all questions on lower airway symptoms. Forty-one workers (23%) experienced coughing, shortness of breath or wheezing at work which improved during vacations/weekends. The prevalence of the work-related asthma symptom complex was 15% ($n = 27$).

Table III. Prevalences according to different criteria for interview- (I–IV) and questionnaire- (QI–QII) derived OcR, sensitization to occupational allergens and relation to "asthma symptom complex" and "work-related asthma symptom complex" among 183 bakery workers.

			OR (95% CI)	
OcR category	*n* (%)[a]	Occupational sensitization; *n* (%)[b]	Asthma symptom complex	Work-related asthma symptom complex
I	42 (23)	18 (43)	5.05 (2.2–11.8)	3.66 (1.5–8.9)
II	55 (30)	21 (38)	4.29 (1.9–9.9)	3.40 (1.4–8.2)
III	64 (35)	29 (45)	7.06 (2.9–17.0)	4.26 (1.7–10.4)
IV	91 (50)	36 (40)	6.17 (2.3–16.6)	3.17 (1.2–8.3)
QI	61 (34)	24 (39)	8.25 (3.4–20.0)	5.04 (2.1–12.4)
QII	77 (43)	29 (38)	9.65 (3.6–26.2)	4.82 (1.8–12.6)

[a]Percentage of total cohort.
[b]Percentage of OcR category.

IgE sensitization

The most frequent causes of suspected occupational sensitization were different species of storage mites. Thirty-seven workers (20%) were sensitized to A. siro, L. destructor or T. putrescentiae. Thirty (16%) were sensitized to A. siro. Of the 23 workers (13%) sensitized to L. destructor, 16 were also sensitized to A. siro. All of those sensitized to T. putrescentiae were sensitized to L. destructor, and five out of six to A. siro. Only half of those (15/30) sensitized to A. siro were sensitized to D. pteronyssinus. Twenty-three percent (34/149) of the production workers were sensitized to storage mites, but only 6% (2/34) of the administrative staff (OR 4.73; CI 1.10–42.53; crude exact CI).

Twenty-two workers (12%) were sensitized to wheat, 13 of whom were additionally sensitized to timothy. All individuals sensitized to rye, barley or oats ($n=18$; 10%) were also sensitized to wheat (Table V).

Testing for birch, dog, cat, dust mite (D. pteronyssinus) and timothy revealed that 53 employees (29%) were positive for at least 1 of these allergens.

OcR and IgE sensitization

Associations between OcR-III and -IV and sensitization to an occupational allergen were found after adjusting for sensitization to common aeroallergens, the strongest being to OcR-III (OR 2.33; CI 1.13–4.81). No association was found between OcR-I and -II and occupational sensitization.

In crude bivariate analysis, the categories OcR-I and -III were associated with storage mite sensitization: OR 2.38; CI 1.07–5.29 and OR 2.30; CI 1.09–4.87, respectively. This effect was sustained for OcR-I when adjusting for sex, smoking and length of service (OR 2.38; CI 1.02–5.52). After adjustment for age, the effect disappeared. When considering individuals with storage mite sensitization, but excluding those who were D. pteronyssinus-sensitized, the association for OcR-I was significant even after adjusting for all confounders (sex, smoking, age and length of service): OR 4.40; CI 1.53–12.68.

The proportion of occupational sensitization in the different categories of OcR varied between 38% (OcR-II) and 45% (OcR-III) (Table III). All the categories of non-IgE-mediated (non-IgE) OcR were

Table IV. Prevalences of lower airway symptoms as categorized by the ECRHS questions in bakery workers ($n=180$) and in a Norwegian population ($n=3315$).

In the last 12 months have you experienced	Bakers; *n* (%)	Norwegian population; *n* (%)	Crude OR (95% CI)
Wheezing	63 (35)	796 (24)	1.70 (1.2–2.3)
Wheezing with breathlessness	47 (26)	431 (13)	2.37 (1.7–3.4)
Wheezing without a cold	43 (24)	497 (15)	1.78 (1.3–2.5)
Waking with chest tightness	43 (24)	366 (11)	2.53 (1.8–3.6)
Breathlessness at night	18 (10)	166 (5)	2.11 (1.3–3.5)
Cough at night	54 (30)	862 (26)	1.22 (0.9–1.7)
Asthma symptom complex	34 (19)	298 (9)	2.36 (1.6–3.5)
Diagnosed asthma:			
Asthma attack	11 (6)	99 (3)	2.11 (1.1–4.0)
Current asthma medication	14 (8)	99 (3)	2.74 (1.5–4.9)
Doctor's diagnosis of asthma	16 (9)	166 (5)	1.85 (1.1–3.2)
Previously diagnosed asthma	4 (2)	99 (3)	0.74 (0.3–2.0)

Table V. Prevalences of IgE sensitization in 183 bakery workers. The values shown represent numbers of patients, with percentages in parentheses.

Agent	Total	SPT	Serum-specific IgE	Histamine release test
A. siro	30 (16)	16 (9)	15 (8)	9 (5)
L. destructor	23 (13)	9 (5)	12 (7)	9 (5)
T. putrescentiae	6 (3)	–	6 (3)	–
Wheat	22 (12)	7 (4)	20 (11)	5 (3)
Rye	18 (10)	2 (1)	18 (10)	2 (1)
Barley	18 (10)	6 (3)	14 (8)	5 (3)
Oats	10 (6)	1 (1)	9 (5)	0
α-amylase	13 (7)	13 (7)	4 (2)	1 (1)
B. germanica	5 (3)	–	5 (3)	–
Soybean	3 (2)	–	3 (2)	–
C. herbarium	0	0	0	0
Timothy	38 (21)	29 (15)	27 (15)	11 (6)
D. pteronyssinus	25 (14)	–	25 (14)	–
Birch	18 (10)	–	18 (10)	–
Cat	6 (3)	–	6 (3)	–
Dog	8 (4)	–	8 (4)	–

associated with the asthma symptom complex, the strongest effect being observed for non-IgE OcR-I (OR 6.55; CI 2.30–18.45), but not with the work-related asthma symptom complex. IgE-mediated OcR was clearly associated with the work-related asthma symptom complex, the strongest effect being observed for IgE OcR-III (OR 5.87; CI 2.12–15.76), but only IgE OcR-III and -IV were associated with the asthma symptom complex.

Discussion

The various diagnostic criteria used make it difficult to evaluate the quality of, and correlate the results from, different studies of OcR among bakery workers. In the ICR [4] there appear to be two definitions of rhinitis. The first is "Inflammation of the lining of the nose, characterized by one or more of the following symptoms: nasal congestion, rhinorrhoea, sneezing and itching". The extent of mucosal inflammation in the nose is difficult to assess objectively in a reproducible way in an occupational setting. Accordingly, we have chosen to base our criteria and rhinitis categories on the exclusively symptoms-related definition of the ICR, as described in the Material and methods.

Recently [19], the consequences of claiming one, two, three or four nasal symptoms for the diagnosis of rhinitis have been demonstrated. In the present study we have distinguished between one or two rhinitis symptoms and whether or not the symptoms are present for 1 h per day on most days. The category closest to the definition of the ICR is the one we have termed OcR-I.

The ICR criteria may be too strict, and may exclude employees with work-related, chronic nose problems. Particularly, the criterion of persistent nose symptoms for >1 h per day on most days is not easy to apply within an occupational setting. Firstly, the employees are not at work all day. Secondly, many bakers always have to clear their nose as a result of secretions/crusts at the end of the day, but are doubtful whether they are affected by a blocked or runny nose for >1 h most days. Thirdly, the nose symptoms of OcR very often arise abruptly when certain elements in the production process are encountered. If the employee manages to avoid the triggering factor for some days it is difficult for him/her to state that he/she is affected by nose symptoms on most days.

The term "occupational rhinitis" should be used when the cause is found in the working environment or when it arises as a direct consequence of work. In a study [20] in which airway symptoms were investigated in people working with low-molecular-weight isocyanate compounds, OcR (questionnaire-derived) was defined as "at least one of three nasal symptoms (runny nose, congestion and sneezing), which improves on weekends or vacations". With this definition the authors seem to expect the symptoms always to subside when leaving the workplace at weekends or when on vacation. This may not be the case when OcR has become chronic. We therefore suggest adding the criteria "trigger factor" and/or "without any nose symptoms before employment" when defining work-related rhinitis.

The diagnosis of OcR in The Finnish Register of Occupational Diseases [5] necessitates "work-related symptoms, sensitization to a specific agent at work, a positive nasal challenge test to this agent, and the exclusion of other reasons for rhinitis". These strict criteria imply that mainly cases of IgE-mediated allergic OcR are included, and that probably most cases of non-IgE-mediated OcR are

excluded. In a Dutch study [21], it was found that only 30% of symptomatic bakers were sensitized to an occupational allergen. In our study, 38–45% of those diagnosed as having OcR (depending on the criteria used) were sensitized to 1 or more of the tested occupational allergens. In a recent article [22], persistent, non-IgE-mediated rhinitis was shown to be an independent risk factor for asthma. In the present study we found an association between the non-IgE-mediated OcR categories and the questionnaire-derived asthma symptom complex, the strongest effect being observed for non-IgE-mediated OcR-I. Accordingly, it seems important to recognize individuals with non-IgE-mediated OcR and to consider them to be at risk of contracting lower airway symptoms and asthma, as we do for individuals with IgE-mediated OcR.

The absence of an association between the categories OcR-I and -II and sensitization to the occupational allergens stresses the need for a greater awareness of non-IgE-mediated OcR. These rhinitis categories are based on the strictest diagnostic criteria.

In a review of baker's asthma from 1999 [7], rhinitis was considered to be "a pre-stage of asthma". Our finding that nose symptoms preceded those of the lower airway supports this view. Baker's asthma is regarded as the worst outcome of flour dust exposure. However, during a 2-year follow-up period, five workers had to leave their jobs due to work-related rhinitis, conjunctivitis and/or skin problems, and none as a result of asthma.

Using questionnaires, most authors have chosen a definition claiming only one of three rhinitis symptoms for OcR [1,3,20], which in the present study would have yielded a prevalence of 42%. When claiming 2 of 3 rhinitis symptoms we found a prevalence of 24%, and this criterion is probably closer to the intention of the ICR when searching for a questionnaire-derived diagnosis of OcR.

In our definitions of OcR we may have included cases of previously acquired rhinitis (intermittent or persistent IgE-mediated allergic rhinitis or persistent non-IgE-mediated rhinitis) who experienced deterioration of nose symptoms at work. If an employee reacts to a new agent in the working environment, and this agent triggers symptoms, we should perhaps consider this to be true OcR. Otherwise, the term "work-aggravated rhinitis" may be used, corresponding to the term work-aggravated asthma [23].

We found a higher prevalence of lower airway symptoms when comparing our population of bakers with a random Norwegian population investigated in 1991 [16]. That cohort was aged 20–44 years, matching our population fairly well. The differences are probably not solely attributable to a lack of adjustment for smoking and a general increase in airway diseases and allergy, but are also attributable to the hazards of working in an atmosphere of flour dust. As identical questionnaires were used, employees in bakeries are suggested to have a greater frequency of lower airway symptoms, especially those that are asthma-related, than the general population.

Twenty percent of our population were sensitized to storage mites. In a general population study from Gotland, Sweden [24], the prevalence of storage mite sensitization was 6.8% in 1984, increasing to 8.1% in 1991. In a study from an urban area on the west coast of Norway [25] it was found that 12.5% of outpatients examined for allergy had a positive skin reaction to a storage mite. The high prevalence of storage mite sensitization that we found compared to other studies may in part be attributed to the higher diagnostic strength of our study, in which we used a wider range of allergic tests. However, the main reason is probably that storage mites are prevalent in bakeries in the western part of Norway.

Conclusions

We have demonstrated in this study that using different criteria for the diagnosis of OcR has considerable consequences for the estimated prevalence of the disease. A consensus on the diagnostic criteria for OcR is needed from clinical, scientific and legal points of view. It should include two out of three main nose symptoms in order to be in line with the 1994 ICR. It should also indicate whether improvement when not at work or the presence of a trigger factor in the working environment is experienced.

Both IgE- and non-IgE-mediated OcR are strongly associated with lower airway symptoms, and possibly asthma. By increasing awareness of OcR we may prevent the development of asthma and the early retirement of bakery workers.

Based on this study from Western Norway, storage mites seems to be important allergens in bakeries, with A. siro being the most important representative.

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Paper II

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Nasal indices of eosinophilic and exudative inflammation in bakery-workers

Torgeir Storaas, Laila Årdal, Thien Van Do, Erik Florvaag, Sverre K. Steinsvåg, Ågot Irgens, Tor B. Aasen and Lennart Greiff

Abstract

Aims: Rhinitis symptoms frequently occur in bakery-workers. Yet, little is known about the pathophysiology of this condition. The objective of the present study was to examine nasal indices of inflammation in relation to occupational dust exposure, occupational rhinitis according to defined criteria, rhinitis symptoms associated to the workplace, and occupational sensitization in bakery-workers. Methods: Bakery-workers (n ¼ 197) were subjected to interviews, questionnaires, workplace dust measurements, allergy tests, and nasal lavages with and without histamine. a2-Macroglobulin and eosinophil cationic protein (ECP) were measured in saline lavages as indices of plasma exudation and eosinophilic activity, respectively. Histamine lavages were employed to explore the nasal exudative responsiveness.

Results: a2-Macroglobulin and ECP increased significantly by increased workplace dust exposure (P£0Æ035). Furthermore, the exudative responsiveness to histamine increased significantly by such exposure (P£0Æ016). Similar patterns were seen in workers with occupational rhinitis and in subjects with rhinitis symptoms associated to the workplace, but not in workers with occupational sensitization.

Conclusions: We conclude that occupational dust exposure in bakery-workers is associated with nasal eosinophilic exudative inflammation. In contrast, occupational sensitization is not a discriminating factor with regard to indices of eosinophilic, exudative inflammation in the present material.

Key words

a2-macroglobulin; airway; allergy; eosinophil cationic protein; flour; occupational rhinitis

Paper III

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Bronchial responsiveness in bakery workers: relation to airway symptoms, IgE sensitization, nasal indices of inflammation, flour dust exposure and smoking

Torgeir Storaas, Ågot Irgens, Erik Florvaag, Sverre K. Steinsvåg, Laila Årdal, Thien Van Do, Lennart Greiff and Tor B. Aasen

Abstract

Background: Bronchial hyperresponsiveness (BHR) is common in bakery workers. The relation between bronchial responsiveness measured with a tidal breathing method and smoking, airway symptoms, IgE-sensitization, nasal indices of inflammation and flour dust exposure have been studied with bronchial responsiveness expressed as a continuous outcome.

Material and methods: Bakery workers (n = 197) were subjected to interviews, questionnaires, allergy tests, workplace dust measurements and bronchial metacholine provocation. Eosinophil cationic protein (ECP) and a2-macroglobulin were measured in nasal lavage. Bronchial responsiveness was expressed as slopeconc, a measurement based on regressing the per cent reduction in FEV1 at each provocation step.

Results: BHR expressed as slopeconc was associated with smoking (P = 0Æ009), asthma symptoms at work (P = 0Æ001), and occupational IgE sensitization (P = 0Æ048). After adjusting for baseline lung function the association between BHR and IgE sensitization was no longer present. We demonstrated an association between nasal ECP and BHR (slopeconc < 3: P = 0Æ012), but not to a2-macroglobulin in nasal lavage. No association was seen between BHR and current exposure level of flour dust, number of working years in a bakery or a history of dough-making.

Conclusion: BHR is related to baseline lung function, work-related asthma symptoms, smoking and nasal eosinophil activity, but not to occupational IgE sensitization and current flour dust exposure when measured with metacholine provocation. The slopeconc expression seems to be a useful continuous outcome in bronchial responsiveness testing.

Key words

baseline lung function; eosinophil cationic protein; metacholine; nasal lavage; smoking; a2-macroglobulin