# Wheat Sensitization and Work-related Symptoms in the Baking Industry Are Preventable

## An Epidemiologic Study

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**A cross-sectional study was conducted among 393 workers from 21 bakeries to study the relationship between wheat allergen exposure and wheat sensitization and work-related allergic symptoms. Exposure to wheat allergens was characterized by a recently developed and validated immunoassay. Specific IgE antibodies against wheat flour and common allergens were measured by immunoassays, and work-related allergic symptoms were registered by questionnaire. A strong and positive association was found between wheat flour allergen exposure and wheat flour sensitization. This relationship was steepest and strongest in atopics. Prevalence ratios for high and medium wheat allergen exposure were 5.2 (95% confidence interval [CI], 1.6–16.2), and 2.7 (0.5–14.5) for atopic workers, and 2.5 (0.8–7.5) and 1.4 (0.3–6.4) for nonatopics, compared with workers with low wheat allergen exposure. In sensitized bakers those with an elevated allergen exposure had more often work-related symptoms, with prevalence ratios for high and medium wheat allergen exposure of 3.5 (CI 1.6–7.5) and 2.6 (CI 0.9–7.8), respectively, compared with workers with low wheat allergen exposure. The existence of exposure–sensitization gradients suggests that work-related sensitization risk will be negligible when exposure levels will be reduced to average exposure concentration of 0.2 $\mu g/m^3$ wheat allergen or approximately 0.5 $mg/m^3$ inhalable dust during a work shift.** Houba R, Heederik D, Doekes G. Wheat sensitization and work-related symptoms in the baking industry are preventable: an epidemiologic study. AM J RESPIR CRIT CARE MED 1998;158:1499–1503.

Occupational asthma is presently the most prevalent occupational respiratory disorder (1, 2) and more than 200 agents used in occupational environments are known to cause asthma (3). Until now, however, there is only limited insight into the risk factors related to this disease. Asthma is generally considered to be an environmentally acquired disease (4–6), but in most studies quantitative estimates of its contribution have been evaluated only for atopy, a host factor (4). For few agents exposure levels have been evaluated at which workers become sensitized or at which sensitized workers develop symptoms. The main reason is the absence of detailed exposure information, often because no methods existed to quantify this exposure. Recently, methods have been developed for the measurement of some airborne high-molecular-weight allergens (7, 8), which have found an application in epidemiological studies.

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Because of the complex etiology of allergic asthma, exposure levels at which sensitization occurs might differ from concentrations that cause symptoms in already sensitized workers (9). This implies that different types of exposure–response relationships exist. Exposure–sensitization relationships have been studied for a few occupational agents only (10–13). If available, it should be possible to determine exposure levels that would preclude sensitization of workers and would therefore be relevant for the primary prevention of occupational asthma. Sensitized workers may develop symptoms after repeated exposure to possibly very low levels of the sensitizing agent. In workers exposed to high levels of allergens, a higher proportion of the sensitized workers is expected to respond with allergic symptoms compared with groups of workers with lower levels of allergen exposure. Such relationships have hardly been explored, but are important for the development of effective secondary prevention strategies.

We have data available from an epidemiological survey in a group of bakery workers, which allowed the study of these different types of exposure–response relationships for wheat flour allergens.

## METHODS

### Population

The health survey was carried out between April 1991 and July 1993 and comprised 427 production workers from 21 bakeries. The bakeries involved comprised a representative sample of five large industrial

bakeries (40 to 200 employees) and small bakeries (1–6 employees). The participation rate was 75% and nonresponse was mostly due to holidays and non-job-related illnesses. Detailed information about the characteristics of the bakeries can be found elsewhere (14). Informed written consent was obtained from all subjects, according to Dutch legal requirements. Only a small number of workers refused to take part in the study (6% of all eligible workers). Nonresponders were equally distributed among all bakeries and all types of jobs. Maintenance workers were excluded from the analyses because of potential exposures to other respiratory hazards (e.g., welding fumes), leaving 393 bakery workers in the study. From 346 workers, venous blood samples were taken and analyzed for total IgE and specific IgE antibodies, as described subsequently. The other 47 workers were equally distributed over all job titles and the frequency of work-related symptoms in this group was similar compared with the bakers with blood samples (28% versus 22%; $p = 0.38$).

### Questionnaire

All workers completed a short self-administered Dutch version of the internationally accepted British Medical Research Council (BMRC) respiratory questionnaire (15), supplemented with questions on work-related symptoms. Symptoms were considered work-related if they were reported by the subject as being provoked by contact with flour or process-related products (e.g., baking additives) during work ("Do you have any of the following allergic symptoms during work, after contact with certain agents at work?"). Work-related rhinitis was defined as the presence of sneezing or running nose (production of nasal secretions) during work. Work-related conjunctivitis was defined as the presence of itchy or teary eyes. In addition, complete records of smoking habits and job histories were obtained.

### IgE Antibodies

Sera were stored at −20° C until IgE analysis. Specific IgE antibodies to wheat flour were measured with a commercial immunoassay (AlaSTAT;DPC, Apeldoorn, The Netherlands) (16). Sera of class 1 or higher (> 0.35 kU/L) were considered positive. Total IgE and specific IgE antibodies to house dust mite, grass pollen, birch pollen, cat allergen, and fungal α-amylase were measured with previously described enzyme immunoassays (17). The presence of atopy in this study was defined on the basis of IgE serology data. Two parameters were used separately as indicators of atopy: a total serum IgE ⩾ 100 kU/L, and the presence of specific IgE to at least one of the common allergens of the test panel.

### Allergen Exposure Assessment

In all bakeries, personal inhalable dust samples were collected in the workers' breathing zone during full-shift periods of 6 to 8 h (18). Wheat flour was recovered from the filters, and the wheat allergen concentrations were measured by inhibition enzyme immunoassay (EIA) (14). Wheat allergen exposure varied considerably among bakery workers, depending on the job of the bakery worker (e.g., doughmaker or packer) and the type of the bakery (14). Based on these two characteristics, 22 occupational titles could be distinguished (19) and each bakery worker was classified into one of these occupational titles. The 22 job titles were used for further classification into three broader exposure categories as described subsequently.

### Statistical Analyses

All statistical analyses were performed using SAS software (version 6.09). Differences in mean exposure levels were tested using Student's *t* tests (PROC ANOVA). The determinants of work-related respiratory symptoms were analyzed by multiple regression techniques. Prevalence ratios (PRs) were calculated by using a proportional hazards model (Cox's regression using PROC PHREG) (20, 21). For the analysis of the relation between allergen exposure and sensitization, all bakery workers were classified into an exposure category based on their total job history (highest exposed category ever worked in). For the analyses of acute respiratory symptoms, however, the classification into exposure groups was based on the job title in the year prior to the survey. In all analyses, differences with $p < 0.05$ (two-sided) were considered significant.

## RESULTS

### Allergen Exposure Categories

The mean wheat allergen exposure gradually increased over all 22 occupational titles (19). Therefore, three exposure groups were formed with approximately equal number of bakery workers (see Table 1). Some alternative ways of classification have been tested (with different cutoff points), but these produced similar results in the epidemiological analyses. The group with the highest wheat allergen exposure levels (Group 3) consisted mostly of dough makers from the industrialized bakeries including all workers from small traditional bakeries. Group 2 consisted of all-round staff, oven staff, and production managers. All other workers were classified into Group 1. The wheat allergen exposure was significantly different between all groups, and the geometric mean dust exposure values for the three wheat allergen exposure groups were 2.37, 0.78, and 0.46 mg/m$^3$, respectively.

### Population Characteristics

Population characteristics are given in Table 2, including an overview of the prevalence of chronic respiratory symptoms, work-related symptoms, and results of the IgE analyses. Work-related symptoms were highly prevalent among the bakery workers, ranging from 29 bakers (7%) with chest tightness to 83 (21%) with rhinitis. Most workers with chest tightness also reported rhinitis (21 of 29). Because of this highly associated occurrence of different symptoms, subsequent analyses with work-related symptoms were not performed for each symptom separately, but for bakers who reported rhinitis and/or chest tightness. Eighty-seven bakery workers (25%) had total IgE levels ⩾ 100 kU/L. A positive IgE test to any of the four common allergens was found in 94 bakers (27%). Both parameters of atopy were closely associated ($\chi^2 = 43$; $p < 0.001$). Wheat flour–specific IgE was detected in 36 bakery workers (10%) and 26 (7%) had specific IgE to fungal amylase. Only six workers were sensitized to both wheat flour and α-amylase.

### Determinants of Work-related Symptoms (Other than Allergen Exposure)

Variables significantly associated with symptoms were atopy, defined either as elevated total IgE (PR 2.8; 95% confidence interval [CI] 1.8–4.4) or the presence of specific IgE to common allergens (PR 2.6; CI 1.6–4.0). Age, gender, years of employment, and all indicators of smoking habits were not related to work-related respiratory symptoms. Although smoking habits were not related to work-related symptoms, they were positively associated with most of the chronic respiratory symptoms.

**TABLE 1**

**DEFINITION OF EXPOSURE CATEGORIES FOR WHEAT FLOUR ALLERGENS (CONCENTRATIONS IN μg/m$^3$)**

| Exposure Category | n | Samples < Detection Limit | AM | GM | GSD | Range |
|---|---|---|---|---|---|---|
| I* Low | 151 | 38% | 0.2 | 0.1 | 3.1 | 0.03–7.7 |
| II* Intermediate | 120 | 9% | 3.5 | 0.7 | 6.4 | 0.03–74.6 |
| III* High | 178 | 1% | 11.0 | 3.8 | 4.4 | 0.03–252.4 |

*Definition of abbreviations*: n = number of personal samples; AM = arithmetic mean; GM = geometric mean; GSD = geometric standard deviation.

* Exposure significantly different from all other categories ($p < 0.05$).

**TABLE 2**

**CHARACTERISTICS OF THE GROUP OF BAKERY WORKERS (n = 393)**

| | Mean ± SD | | Range |
|---|---|---|---|
| Age, yr | 33.9 ± 9.9 | | 17–61 |
| Years in bakery industry | 9.0 ± 8.1 | | 0.1–43 |
| Years smoked | 10.0 ± 10.1 | | 0–43 |
| Pack-years | 6.5 ± 8.2 | | 0–43 |
| | *n* | % | |
| Smokers | 189 | 48 | |
| Ex-smokers | 85 | 22 | |
| Nonsmokers | 119 | 30 | |
| % Male | 348 | 89 | |
| Chronic respiratory symptoms (n = 393) | | | |
| Chronic cough | 46 | 12 | |
| Chronic phlegm | 26 | 7 | |
| Shortness of breath | 26 | 7 | |
| Ever wheezing | 91 | 23 | |
| Frequent wheezing | 30 | 8 | |
| Chest tightness | 41 | 10 | |
| Work-related symptoms (n = 393) | | | |
| Rhinitis | 83 | 21 | |
| Conjunctivitis | 58 | 15 | |
| Chest tightness | 29 | 7 | |
| IgE serology (n = 346) | | | |
| Total IgE ⩾ 100 kU/L | 87 | 25 | |
| House dust mite | 69 | 20 | |
| Grass pollen | 53 | 15 | |
| Birch pollen | 16 | 5 | |
| Cat allergens | 15 | 4 | |
| Wheat flour | 36 | 10 | |
| Fungal α-amylase | 26 | 7 | |
| Positive IgE response and work-related symptoms (rhinitis and/or chest tightness [n = 346]) | | | |
| Wheat flour | 15 | 4 | |
| Fungal α-amylase | 12 | 3 | |

### Exposure–Sensitization Relationships

Table 3 shows the relationship between wheat allergen exposure and wheat-specific IgE sensitization. A clear exposure–response relationship was found, both for atopic and nonatopic workers. The relationship was steepest within the group of atopic bakers. Atopics with a high and medium wheat allergen exposure were 5.2 (CI 1.6–16.2) and 2.7 (CI 0.5–14.5) times more likely to be sensitized to wheat allergens compared with workers with low allergen exposure. Nonatopics with high and medium exposure were only 2.5 (CI 0.8–7.5) and 1.4 (CI 0.3–6.4) times more likely to be sensitized than at low exposure. Several other potential effect modifiers or confounders were tested (smoking habits, gender, age, and years in bakery industry), but none was significantly associated with wheat sensitization. Addition of these variables to the multiple regression models hardly changed the presented prevalence ratios. Similar exposure–sensitization relationships were found in analyses with atopy defined as a positive IgE test to common allergens, or a combination of total and specific IgE.

### Exposure–Symptom Relationships

Table 4 shows the relationship between wheat allergen exposure and work-related symptoms. Work-related symptom prevalence tended to increase with increasing wheat allergen exposure. The strongest exposure–response relationship was found in wheat flour–sensitized workers. The prevalence ratios for high and medium wheat allergen exposure were 3.5 (CI 1.6–7.5) and 2.6 (CI 0.9–7.8) for sensitized workers, and 1.6 (CI 0.9–2.9) and 1.4 (CI 0.8–2.7) for nonsensitized workers, compared with workers with low wheat allergen exposure as the reference group. Addition of any of the potential confounders and modifying factors to the model (atopy, age, gender, and smoking habits) did not change the results.

**TABLE 3**

**PREVALENCE OF WHEAT FLOUR SENSITIZATION (SPECIFIC IgE) BY WHEAT ALLERGEN EXPOSURE CATEGORY AND ATOPY DEFINED AS TOTAL SERUM IgE ⩾ 100 kU/L (n = 346)**

| Wheat Allergen Exposure | Positive IgE for Wheat Flour | |
|---|---|---|
| Whole population (n = 346) | | |
| Low | 4/90 | 4.4% |
| Intermediate | 5/64 | 7.8% |
| High | 27/192 | 14.1% |
| Atopic workers (n = 87) | | |
| Low | 1/22 | 4.6% |
| Intermediate | 2/17 | 11.8% |
| High | 11/48 | 22.9% |
| Nonatopic workers (n = 259) | | |
| Low | 3/68 | 4.4% |
| Intermediate | 3/47 | 6.4% |
| High | 16/144 | 11.1% |

## DISCUSSION

In this study we investigated the prevalence of sensitization and work-related symptoms in relation to wheat allergen exposure in the bakery industry. The likelihood of sensitization increased with increasing wheat allergen concentration in the workplace air. Atopy appeared to be an important effect modifier of this relationship, and the steepest slope between allergen concentration and sensitization rate was found for atopic workers. However, sensitization to wheat flour was also found in nonatopic bakery workers and for this group of workers an exposure–response trend was found as well, but with a less steep slope. In a previous study, strong exposure–sensitization relationships were described for α-amylase allergens using skin prick test as a response variable (11). For α-amylase allergens too, the strength and slope of the exposure–response relationship also differed between atopics and nonatopics, with a steeper exposure–response curve for atopics (11).

The likelihood of the presence of acute work-related symptoms increased with increasing exposure in sensitized workers.

**TABLE 4**

**PREVALENCE OF WORK-RELATED SYMPTOMS (RHINITIS AND/OR CHEST TIGHTNESS) IN RELATION TO WHEAT ALLERGEN EXPOSURE AND WHEAT FLOUR–SPECIFIC SENSITIZATION, AS MEASURED BY SPECIFIC IgE ANTIBODIES (n = 346)***

| Wheat Allergen Exposure | Work-related Symptoms | |
|---|---|---|
| Whole population (n = 346) | | |
| Low | 18/117 | 15.4% |
| Intermediate | 25/107 | 23.4% |
| High | 35/122 | 28.7% |
| Workers sensitized for wheat flour (n = 36) | | |
| Low | 1/7 | 14.3% |
| Intermediate | 4/10 | 40.0% |
| High | 10/19 | 52.6% |
| Workers not sensitized for wheat flour (n = 310) | | |
| Low | 17/110 | 15.5% |
| Intermediate | 21/97 | 21.6% |
| High | 25/103 | 24.3% |

* Because bakery workers were classified in one of these categories based on their actual allergen exposure, rather than on the complete job history, the number of workers in each category differs from the numbers presented in Table 3.

Once sensitized, bakers may develop allergic symptoms upon renewed exposure to the specific allergen. It is often suggested that sensitized individuals may develop attacks of asthma at very low exposure levels. This conclusion, however, is probably mainly based on the experience of patients visiting medical centers for their usually severe asthmatic symptoms. In fact, exposure–symptom relationships for sensitized individuals have not been studied yet in open populations of bakery workers. Our study results suggested that such an exposure-related response might exist within the group of sensitized bakers. The number of sensitized individuals in each exposure category was small, and the results should therefore be interpreted with some caution. Larger and prospective studies in sensitized workers are necessary to confirm these findings. Nevertheless, the suggestion of a positive relationship between exposure and symptoms implicates that symptoms may be avoided in already sensitized workers by removing them from high exposures. Atopy and the level of allergen exposure appeared to be the most important determinants of work-related symptoms, whereas age, gender, and smoking habits were not or only weakly associated with the prevalence of work-related symptoms.

Atopy has been identified as an important risk factor for work-related respiratory symptoms in many other studies (22–26). Relationships of sensitization and symptoms with exposure proxies have been less systematically investigated, but were reported for estimates of dust exposure (25, 27) and for wheat allergen exposure (13). Although work-related symptoms were associated with wheat allergen (and also α-amylase allergen) exposure, not all symptoms could be explained by an IgE response to one of these allergens. In this study 23% of the bakery workers reported work-related rhinitis and/or chest tightness, but in only 30% of this group (7% of all bakery workers) IgE sensitization to wheat or α-amylase could be demonstrated. There are some possible explanations for this finding. First, our IgE assays may have failed to detect sensitization in some individuals, although the sensitivity and specificity were comparable to other assays for measuring IgE. Second, many other allergens have been identified in case series of asthmatic bakers, for instance other cereal flours (28, 29) and several baking additives like soybean flour (30, 31) and other fungal enzymes such as glucoamylase and (hemi)cellulase (31, 32). These allergens may have caused allergic reactions in some bakery workers but it is not very likely that specific sensitization to these occupational allergens can explain all symptoms that cannot be attributed to wheat flour. A nonspecific reaction to the dusty environment in the bakeries is probably an additional explanation as was also suggested in another epidemiological survey (13). This suggests that the group of bakers with work-related respiratory symptoms is probably heterogeneous with regard to the actual cause of these symptoms.

In conclusion, clear exposure–sensitization and exposure–symptom relationships were found for wheat allergens and similar trends were found for α-amylase allergens. The strength and slope of these relationships varied according to the status of the workers (atopy and sensitization). The described exposure–response relationships have important consequences for occupational health care and preventive strategies in the bakery industry. The findings of exposure–response gradients provide important support for causation and suggest that sensitization as well as development of occupational asthma in already sensitized workers is to some extent preventable by reducing exposure levels. At present, no health-based exposure standards exist for occupational wheat allergen exposure. Development of exposure standards for wheat dust in the air is being considered by standard-setting bodies in several countries in the European Union and the American Conference of Governmental Occupational Hygienists. Our results suggest that exposure levels have to be reduced to the average exposure level of the lowest exposure category, 0.2 $\mu g/m^3$ wheat allergen or approximately 0.5 $mg/m^3$ inhalable dust during a work shift, to reduce the sensitization rates of those found in non-wheat-exposed populations (33). This kind of information is extremely important when standard setting is considered for allergen exposure in the bakery and flour milling industries. This implies a sixfold reduction in exposure in our population for highly exposed dough makers in industrialized bakeries and bread bakers. For workers with other job titles, the required reduction factors are less, a factor 2 maximally.

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## References

1. Chan-Yeung, M. 1990. Occupational Asthma (Suppl). *Chest* 98:148S–161S.
2. Meredith, S. K., V. M. Taylor, and J. C. McDonald. 1991. Occupational respiratory disease in the United Kingdom 1989: a report to the British Thoracic Society and the Society of Occupational Medicine by the SWORD project group. *Br. J. Ind. Med.* 48:292–298.
3. Chan-Yeung, M., and J. L. Malo. 1994. Aetiologic agents in occupational asthma. *Eur. Respir. J.* 7:346–371.
4. Burney, P. 1988. Why study the epidemiology of asthma? *Thorax* 43: 425–428.
5. Seaton, A. 1995. Occupational asthma. *In* W. K. C. Morgan and A. Seaton, editors. Occupational Lung Diseases. 3rd ed. W. B. Saunders, Philadelphia.
6. Platt-Mills, T. A. E., R. B. Sporik, M. D. Chapman, and P. W. Heymann. 1995. The role of indoor allergens in asthma. *Allergy* 50:5–12.
7. Reed, C. E., M. C. Swanson, and J. T. C. Li. 1993. Environmental monitoring of protein aeroallergens. *In* I. L. Bernstein, M. Chan-Yeung, J. L. Malo, and D. I. Bernstein, editors. Asthma in the Workplace. Marcel Dekker Inc., New York.
8. Gompertz, D. 1994. Measurement of airborne protein allergens in occupational asthma. *Clin. Exp. Allergy* 24:405–406.
9. Venables, K. M. 1994. Prevention of occupational asthma. *Eur. Respir. J.* 7:768–778.
10. Hollander, A., D. Heederik, and G. Doekes. 1997. Respiratory allergy to rats: exposure–response relationships in laboratory animal workers. *Am. J. Respir. Crit. Care Med.* 155:562–567.
11. Houba, R., D. J. J. Heederik, G. Doekes, and P. E. M. van Run. 1996. Exposure–sensitization relationship for α-amylase allergens in the baking industry. *Am. J. Respir. Crit. Care Med.* 154:130–136.
12. Juniper, C. P., M. J. How, B. F. J. Goodwin, and A. K. Kinshott. 1977. Bacillus subtilis enzymes: a 7-year clinical, epidemiological and immunological study of an industrial allergen. *J. Soc. Occup. Med.* 27:3–12.
13. Cullinan, P., D. Lowson, M. J. Nieuwenhuijsen, C. Sandiford, R. D. Tee, and K. M. Venables. 1994. Work related symptoms, sensitization, and estimated exposure in workers not previously exposed to flour. *Occup. Environ. Med.* 51:579–583.
14. Houba, R., P. van Run, D. Heederik, and G. Doekes. 1996. Wheat antigen exposure assessment for epidemiologic studies in bakeries using personal dust sampling and inhibition ELISA. *Clin. Exp. Allergy* 26: 154–163.
15. Medical Research Council Committee on the Aetiology of Chronic Bronchitis. 1966. Instructions for the use of the questionnaire on respiratory symptoms. Holman Ltd., Dawlish, UK.
16. El Shami, A. S., and O. Alaba. 1989. Liquid-phase in vitro allergen-specific IgE assay with in situ immobilization. *Advances Biosci.* 74:191–201.
17. Doekes, G., J. Douwes, I. Wouters, S. de Wind, R. Houba, and A. Hollander. 1996. Enzyme immunoassays for total and allergen specific IgE in population studies. *Occup. Environ. Med.* 53:63–70.
18. ter Kuile, W. 1984. Vergleichsmessungen mit verschiedenen Geraeten zur Bestimmung der Gesamtstaubkonzentration am Arbeitsplatz: Teil

II. *Staub* 44:211–216.
19. Houba, R., D. Heederik, and H. Kromhout. 1997. Grouping strategies for exposure to inhalable dust, wheat allergens, and -amylase allergens in bakeries. *Ann. Occup. Hyg.* 41:287–296.
20. Lee, J., and K. S. Chia. 1993. Estimation of prevalence rate ratios for cross sectional data: an example in occupational epidemiology. *Br. J. Ind. Med.* 50:861–864.
21. Axelson, O. 1994. Some recent developments in occupational epidemiology. *Scand. J. Work Environ. Health* 20 (special issue):9–18.
22. Rosenberg, N., F. Rameix, G. Demangeat, J. J. Philippon, M. H. Rigault, and T. Schlacther. 1991. Prévalence de l'allergie respiratoire dans la boulangerie-pâtisserie parisienne en 1987. *Arch. Mal. Prof.* 52:33–36.
23. De Zotti, R., F. Larese, M. Bovenzi, C. Negro, and S. Molinari. 1994. Allergic airway disease in Italian bakers and pastry makers. *Occup. Environ. Med.* 51:548–552.
24. Järvinen, K. A. J., V. Pirilä, F. Björksten, H. Keskinen, M. Lehtinen, and S. Stubb. 1979. Unsuitability of bakery work for a person with atopy: a study of 234 bakery workers. *Ann. Allergy* 42:192–195.
25. Hartmann, A. L. 1986. Berufsallergien bei Bäckern - Epidemiologie; Diagnose, Therapie und Prophylaxe; Versicherungsrecht. Dustri-Verlag Dr. Karle Feistle, München-Deisenhofen.
26. Prichard, M. G., G. Ryan, B. J. Walsh, and A. W. Musk. 1985. Skin test and RAST responses to wheat and common allergens and respiratory disease in bakers. *Clin. Allergy* 15:203–210.
27. Musk, A. W., K. M. Venables, B. Crook, A. J. Nunn, R. Hawkins, and G. D. Crook. 1989. Respiratory symptoms, lung function, and sensitization to flour in a British bakery. *Br. J. Ind. Med.* 46:636–642.
28. Sutton, R., J. H. Skerritt, B. A. Baldo, and C. W. Wrigley. 1984. The diversity of allergens involved in baker's asthma. *Clin. Allergy* 14:93–107.
29. Thiel, H., and W. T. Ulmer. 1980. Baker's asthma: development and possibility for treatment. *Chest* 78:400–405.
30. Jorde, W., N. Heyer, and M. Schata. 1986. Bäckereirohstoffe als berufsspezifische Allergene. *Allergologie* 9:s552–524.
31. Baur, X., W. Sauer, and W. Weiss. 1988. Baking additives as new allergens in baker's asthma. *Respiration* 54:70–72.
32. Quirce, S., M. Cuevas, M. L. Díez-Gómez, M. Fernández-Rivas, M. Hinojosa, and R. González. 1992. Respiratory allergy to *Aspergillus*-derived enzymes in baker's asthma. *J. Allergy Clin. Immunol.* 90:970–978.
33. Gautrin, D., C. Infante-Rivard, T. V. Dao, M. Magnan-Larose, D. Desjardins, and J. M. Malo. 1997. Specific IgE-dependent sensitization, atopy, and bronchial hyperresponsiveness in apprentices starting exposure to protein-derived agents. *Am. J. Respir. Crit. Care Med.* 155: 1841–1847.