

Incidence and Determinants of IgE-mediated Sensitization in Apprentices

A Prospective Study

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We investigated prospectively the incidence and determinants of work-related specific skin sensitization in a cohort of 769 apprentices, including 417 in animal health technology, 230 in pastry-making, and 122 in dental-hygiene technology. Subjects were recruited when starting exposure to laboratory animals, flour, or latex. A questionnaire and skin-prick tests with common and work-related allergens were administered on entry and at follow-up visits from 8 to 44 mo; information on number of hours of exposure to specific allergens was obtained. Among 769 apprentices, 698 attended ≥ 1 follow-up visit. A total of 111 subjects developed specific sensitization over the study period. The incidence of work-related sensitization (per person-year) was 8.9% (95% CI 7.3 to 11.0%) in the animal-health program, 4.2% (95% CI 1.8 to 8.2%) in the pastry-making program, and 2.5% (95% CI = 0.7 to 4.3%) in the dental-hygiene program. In the animal health group, Cox regression analyses showed that atopy, nasal, and respiratory symptoms in the pollen season, and exposure assessed by the school attended or by duration of exposure to rodents were the most significant predictors of sensitization. In the dental-hygiene program, atopy and asthma were significant determinants. This study shows that: (1) an apprenticeship in animal-health technology carries a greater risk of developing specific sensitization than do apprenticeships in pastry-making and dental-hygiene; (2) atopy, respiratory symptoms in the pollen season, and number of hours in contact with rodents determine the risk of sensitization in apprentices in the animal health program.

The natural history of asthma can be advantageously examined in the context of exposure to occupational aeroallergens causing IgE-mediated sensitization. A number of epidemiologic studies, mostly cross-sectional, have been carried out in workforces exposed to laboratory animals (1–5), flour (6, 7), and latex (8–10). Prospective studies exploring incidence are much less common and, as far as we know, no prospective study has yet been carried out on subjects beginning apprenticeships entailing exposure to high-molecular-weight aeroallergens. Moreover, there has been no documentation of the incidence of sensitization to the antigen relevant to the milieu by comparison with the incidence in subjects in other workforces but not exposed to these agents.

We previously described the baseline characteristics of 769 apprentices exposed for the first time to animal-, flour-, and latex-derived allergens. We now evaluate the incidence and the determinants of the development of IgE-mediated specific sensitization in an effort to describe part of the natural history of both asthma and occupational asthma.

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METHODS

Baseline characteristics of 769 apprentices (417 in animal health technology, 230 in pastry-making, and 122 in dental hygiene technology) recruited in 14 different specialized schools (five in animal health technology, two in dental hygiene, and seven in pastry-making) between 1993 and 1995 have been published (11). Briefly, subjects in these schools were eligible provided that they had not been exposed to the aeroallergens relevant to this study in the course of an apprenticeship or a job for a total of three or more months before entering the program, as assessed in a preliminary visit. The first assessment took place on average 1.4 mo after the program started. The apprentices were reassessed 20, 32, and 44 mo after starting the career program for animal health technology; these intervals were 20 and 32 mo for dental hygiene technology and 8 and 16 mo for pastry-making.

At the time of entry into the apprenticeship program and at each follow-up visit, each student answered a respiratory questionnaire derived from the standardized questionnaire of the International Union Against Tuberculosis and Lung Diseases (IUATLD) (12). Information was obtained on physician-diagnosed asthma, personal allergic conditions, and familial asthma. Symptoms suggestive of asthma included wheezing, chest tightness, shortness of breath, or cough under usual conditions or under such conditions as exercise or exposure to cold air, strong odors, smoke, or dusts. Respiratory symptoms and rhinoconjunctivitis on contact with pets and pollens were also documented. The school attended was used as a surrogate for exposure characteristics. In addition, for the animal health program, the number of hours spent in contact with rodents was considered as a potential determinant for the development of sensitization (13).

Skin tests were done with the prick method (14) using 11 common inhalants: mixed trees, mixed grass, and ragweed pollens; *Alternaria*, *Aspergillus*, and *Hormodendrum*; feathers; *Dermatophagoides farinae* and *pteronyssinus*; and cat and dog dander (Omega, Montreal, PQ, Canada). Mite extracts and cat dander were standardized. All extracts were glycerinated to prevent significant loss of antigenicity. Histamine phosphate (1/200 g/ml) was used as a positive control, and diluent (glycerine, 50%), as a negative control. The largest wheal diameter was assessed 10 to 15 min after introduction of the antigen. A positive reaction was defined as a wheal ≥ 3 mm in the absence of reaction to the diluent and in the presence of a positive reaction to histamine phosphate. Atopy was defined as at least two positive reactions to the common inhalants.

In addition, skin-prick tests were performed with extracts from aeroallergens potentially present in the working areas of students registered in the three career programs. These consisted of urinary proteins from rat, mouse, and rabbit (Pharmacia Allergon AB, Angelholm, Sweden), and hamster, guinea-pig, and rabbit dander (Omega) in laboratories frequented by students in animal health technology or veterinary medicine; mixed flours, wheat, and bran flour, as well as α -amylase (Omega) in pastry-making workshops; and latex (Omega and Stallergenes, Institut Pasteur, Paris, France) from gloves used by students in dental hygiene technology.

The extracts were obtained in amounts sufficient to perform the total estimated number of skin tests for this project; it was ensured that the allergens were produced from the same batches.

Skin-prick tests with these specific allergens were administered to all participants, whatever their career program (except α -amylase, which was administered only to pastry-makers). The skin-prick tests were performed by the same nurse throughout the study.

Subjects who showed sensitization to a work-related antigen at the initial visit were also followed to detect possible new sensitization to another work-related allergen.

Statistical Analysis

Chi-square analysis was used to compare the number of incident cases of sensitization to career-related allergens (defined *a priori*) in the corresponding program to the number of new cases in the other two programs combined. The incidence of program-specific sensitization was expressed in person-years. A Cox proportional hazards model was used for the animal health program to evaluate the effect of the factors on the time to occurrence of the specific sensitization, with the time variable defined as the difference between time of first occurrence of a given event and time of entrance into the program. Fixed covariates in the analysis were assessed at baseline: atopy and immediate skin reaction to pets, history of hay fever, asthma, exercise-induced respiratory symptoms, cold-air-induced respiratory symptoms, rhinitis on contact with pets, respiratory symptoms in the pollen season, and asthma in father as well as two proxies for exposure. These were the number of hours spent in contact with rodents up to an event for which three categories were set (≤ 16 , 17 to ≤ 52 , > 52 h) that best delineated the frequency distribution (Model 1), and the school attended (Model 2). For these fixed covariates, the proportionality assumption was tested using Harrell's procedure on Schoenfeld residuals as provided in S-PLUS for Windows (version 4.5; MathSoft Inc., Seattle, WA). Each exposure proxy was considered separately, in Model 1 and Model 2, that were otherwise similar. Univariate analyses were first carried out for each program; we used the $-2 \log$ likelihood test as the criterion to retain variables for the multivariate analyses. Rate ratios (RR) and 95% confidence intervals (CI) were estimated. Statistical analyses were performed using the SPSS software package (version 7.5 for Windows, Chicago, IL) and S-PLUS. The level of statistical significance for chi-square analyses was set at $p < 0.05$ (two-sided).

RESULTS

Of a total of 769 apprentices who were first assessed (11), 698 attended at least one of the follow-up visits; of these, 690 had interpretable skin-test results and were included in the analy-

ses. Eighty-nine subjects did not complete their training programs; of these, 71 did not attend the first follow-up visit. In animal health technology, 91.3% of those who entered the study attended the 8-mo assessment, and 88.2%, 87.8%, 87.3% the 20-, 32-, and 44-mo assessments, respectively. For dental hygiene technology, 89% of students participated in the 20-mo assessment and 82% in the 32-mo one. Finally, for pastry-making, 82% of students came to the 8-mo assessment and 60% to the 16-mo visit. Table 1 gives the general baseline characteristics and features of general and specific respiratory symptomatology of participants in the initial cohort and of subjects included in the analyses.

The number of subjects who showed sensitization to each of the work-related allergens on entry and any time until the end of the program, without consideration of the duration of the program per se, is presented in Table 2. The subjects considered at risk were those attending at least one follow-up visit and having interpretable results of skin testing ($n = 690$). The proportions of subjects who developed new sensitization were significantly higher in the case of rabbit dander, rabbit urine, rat urine, and mouse urine among animal health apprentices than among the other two groups of subjects. The proportions of students who developed new sensitization for each of the three work-related pastry-making antigens were not significantly different among the three groups. No subject was sensitized to α -amylase. Finally, the proportion of subjects who became sensitized to latex was significantly higher among dental hygiene students than among students in the other two programs. Because a number of subjects developed new sensitization to occupational allergens to which they were not exposed in their career programs (e.g., flour allergens in the animal health and dental hygiene programs, animal-derived allergens in the pastry-making and dental hygiene programs, and latex in the pastry-making program), a new definition for cases of specific sensitization was set *a posteriori*. A subject was considered as a new case if he or she developed sensitization to at least one work-related allergen and if the proportion of sensi-

TABLE 1
BASELINE CHARACTERISTICS OF PARTICIPANTS IN THE INITIAL COHORT AND OF
SUBJECTS PRESENT ON FOLLOW-UP* ASSESSMENT BY TRAINING PROGRAM

	Animal Health		Pastry-making		Dental Hygiene	
	Initial Cohort	Present at Follow-up	Initial Cohort	Present at Follow-up	Initial Cohort	Present at Follow-up
n	417	394	230	186	122	110
General						
Sex, M/F (n)	57/360	55/239	56/174	44/142	2/120	1/109
Age, yr, mean $\pm$ SD	19.6 $\pm$ 3.2	19.5 $\pm$ 2.9	27.8 $\pm$ 10.0	27.2 $\pm$ 9.9	21.3 $\pm$ 5.2	21.6 $\pm$ 5.4
Atopy, n (%)	167 (40.4%)	158 (40.1%)	106 (47.7%)	87 (46.8%)	53 (43.4%)	47 (42.7%)
Hay fever, [†] n (%)	32 (7.7%)	29 (7.4%)	28 (12.2%)	24 (12.9%)	17 (13.9%)	15 (13.6%)
Asthma, [†] n (%)	41 (9.8%)	36 (9.1%)	30 (13.0%)	26 (14.0%)	11 (9.0%)	10 (9.1%)
Smokers	54 (12.9%)	50 (12.7%)	36 (15.6%)	28 (15.1%)	12 (9.8%)	10 (9.1%)
Specific respiratory symptomatology						
Wheezing	74 (17.7%)	68 (17.3%)	50 (21.7%)	41 (22.0%)	15 (12.3%)	14 (12.7%)
Dyspnea	72 (17.3%)	66 (16.8%)	53 (23.0%)	42 (22.6%)	20 (16.4%)	17 (15.5%)
Awakening with cough	16 (3.8%)	14 (3.6%)	18 (7.8%)	14 (7.5%)	3 (2.5%)	2 (1.8%)
Exercise-induced	85 (20.4%)	79 (20.1%)	61 (26.5%)	50 (26.9%)	19 (15.6%)	16 (17.3%)
Cold-air-induced	65 (15.6%)	58 (14.7%)	56 (24.3%)	45 (24.2%)	15 (12.3%)	15 (13.6%)
Rhinitis with pets	123 (29.5%)	115 (29.2%)	89 (38.7%)	71 (38.2%)	47 (38.5%)	40 (42.7%)
Respiratory symptoms with pets	27 (6.5%)	25 (6.3%)	19 (8.3%)	16 (8.6%)	11 (9.0%)	5 (4.5%)
Respiratory symptoms in the pollen season	16 (3.8%)	15 (3.8%)	12 (5.2%)	11 (5.9%)	5 (4.1%)	4 (3.6%)

* Present at at least one follow-up visit and with skin-test results.

[†] Physician-based diagnosis.

TABLE 2
NUMBER OF SENSITIZED SUBJECTS AT BASELINE (PREVALENCE) AND OF NEW CASES
OVER THE FOLLOW-UP PERIOD* (CUMULATED INCIDENCE) OF IGE-MEDIATED SENSITIZATION TO
PROGRAM-RELATED ALLERGENS AND TO SELECTED COMMON AEROALLERGENS BY TRAINING PROGRAM

	Animal Health (n = 394)		Pastry-making (n = 186)		Dental Hygiene (n = 110)		p Value†
	At Baseline	New Cases	At Baseline	New Cases	At Baseline	New Cases	
Program-related allergens							
Rabbit dander	(10)	(30)	2	3	5	4	< 0.01
Guinea-pig dander	(9)	(26)	3	8	0	4	0.14
Hamster dander	(28)	(19)	18	9	11	4	0.9
Rabbit urine	(7)	(22)	0	0	4	5	0.02
Rat urine	(14)	(62)	5	11	2	18	0.02
Mouse urine	(9)	(28)	6	7	3	9	0.06
Wheat flour	4	4	(8)	(5)	1	3	0.2
Mixed flour	0	3	(2)	(2)	0	1	0.7
Bran flour	3	5	(6)	(3)	4	2	0.8
Latex	3	4	1	3	(0)	(7)	< 0.01
Common aeroallergens							
Cat dander	(51)	(35)	36	17	19	11	0.35
Dog dander	(42)	(36)	21	10	13	14	0.08
Grass pollen	89	13	(63)	(7)	26	6	0.53

* Two to four years according to the training program.

† p Values in chi-square analysis comparing the number of new cases of sensitization in the program corresponding with the given antigen (in parentheses) and the sum of new cases with sensitization to the same antigen in the other two programs. Eight subjects refused skin testing or had uninterpretable results.

tized subjects to this allergen, at the end of the study period, was significantly greater in his or her program than in the other two (*a posteriori* definition). These other two groups were assumed to reflect sensitization to the allergen (laboratory animal, flour, latex) in a general population of young adults. In the animal health program, the *a posteriori* defini-

tion of a case was used in the analyses, as two allergens set *a priori* as specific (guinea pig dander and hamster dander) were not found to be so according to the *a posteriori* definition.

As shown in Table 3, immunologic sensitization to at least one of the program-related allergens was documented in 8.6% of subjects on entry; among animal health apprentices, this

TABLE 3
NUMBER OF CASES AND RATES OF PROGRAM-RELATED SPECIFIC SENSITIZATION BY TRAINING PROGRAM

	Animal Health (n = 395)		Pastry-making (n = 186)	Dental Hygiene (n = 109)
	A Priori Definition*	A Posteriori Definition*		
Program-related sensitization on entry (1)				
n	49	31	10	0
Proportion by number at risk	12.4%	7.9%	5.4%	0%
Program-related sensitization on entry without change during follow-up (2)				
n	25	13	10	0
Proportion by number at risk	6.4%	3.3%	5.4%	0%
Program-related sensitization on entry and incident sensitization during follow-up (3)				
n	24	18	0	0
Proportion by number at risk	6.1%	4.0%	0%	0%
Rate by person-year	2.2%	1.7%	—	—
No program-related sensitization on entry and incident sensitization during follow-up (4)				
n	72	67	8	7
Proportion by number at risk	18.2%	17.0%	4.3%	6.4%
Rate by person-year	6.7%	6.2%	4.2%	2.5%
Total number of incident cases of program-related sensitization (5)†				
n	96	85	8	7
Proportion by number at risk	24.3%	21.5%	4.3%	6.4%
Rate by person-year	8.9%	7.9%	4.2%	2.5%

* Number and rates are presented (1) for cases of specific sensitization using the *a priori* definition (i.e., all sensitized cases), (2) for cases of specific sensitization using the *a posteriori* definition (i.e., subjects who developed sensitization to the program-related allergens shown to be relevant to the training program from the results presented in Table 2 [i.e., excluding guinea-pig dander, hamster dander]).

† Sum of lines 3 and 4.

proportion was almost double that found in pastry-making students. None of the subjects entering the dental hygiene program was sensitized to latex on entry. Thirty-five subjects, including 25 in the animal health program and 10 in the pastry-making program, were sensitized to at least one program-specific allergen on entry and had not developed extrasensitization at the time of follow-up. Twenty-four subjects, all in the animal health program, had developed at least one extrasensitization to the six *a priori* defined work-related allergens (animal dander and urine) at follow-up. A total of 87 subjects without program-related sensitization on entry—the majority in the animal health program ($n = 72$)—had developed new sensitization at follow-up. The incidence density of work-specific sensitization over the follow-up period was 8.9% (96/1,075 person-years) (95% CI = 7.3 to 11.0%) in the animal health program (7.9%, 85/1,075 person-years, 95% CI = 6.4 to 9.9% in the case of *a posteriori* definition), 4.2% (8/192 person-years, 95% CI = 1.8 to 8.2%) among pastry-makers, and 2.5% (7/282 person-years, 95% CI = 0.7 to 4.3%) in the dental-hygiene program.

A greater proportion of subjects with incident work-specific sensitization reported incident nose and/or eye work-related symptoms during the follow-up than subjects without; the numbers were 51.8% (44/85) versus 21.7% (64/295) in the animal health group, 25.0% (2/8) versus 8.9% (15/168) in the pastry-making group, and 28.6% (2/7) versus 9.7% (10/103) in the dental hygiene group. The same was found for new work-related respiratory symptoms in the animal health group where 11 of 85 (12.9%) subjects with incident-specific sensitization reported new chest symptoms compared with subjects without (11/295, 3.7%), no apprentice pastry-maker reported new chest symptoms, and only one of seven apprentice dental hygienists did.

Data for total number of hours of exposure to the specific allergens are presented by program and by school in Table 4. In the animal health program, results are shown by school, as a large variation was observed. School no. 5, in which students had the minimum number of hours of exposure to rodents, was considered as the reference category in the univariate Cox regression analysis (Table 5).

Significant determinants of time to sensitization from univariate Cox regression analyses included atopy in all three programs, respiratory symptoms of allergy and suggestive of

asthma in the animal health program, symptoms of rhinoconjunctivitis in the animal health and pastry-making programs, and asthma in the dental hygiene program (Table 5). Familial asthma was related to the development of sensitization to flour-derived allergens. In the animal health program, women were more likely to be sensitized (RR = 3.8, 95% CI = 1.3 to 10.9), whereas no significant effect of age was seen when comparing subjects with < 19 yr (median age) with those ≥ 19 (RR = 0.7, 95% CI = 0.4 to 1.1); current smoking was not a significant factor (RR = 1.0, 95% CI = 0.48 to 2.0) (not shown). As presented in Table 5, spending more than 52 h in contact with rodents was a significant determinant for the likelihood of sensitization; school no. 1 was the school with the highest RR when compared with the reference school (no. 5).

Table 6 gives the results of the multivariate Cox's regression analysis of selected factors (those significant in the univariate analysis) on the development of program-related sensitization (*a posteriori* definition) in the animal health program. Atopy and respiratory symptoms in the pollen season, as well as spending more than 52 h in contact with rodents were all significantly associated with the likelihood of becoming sensitized to at least one work-related allergen (Model 1). In a separate analysis (Model 2) in which the same fixed covariates were used, and school as the exposure proxy, attending school no. 1 was associated with the risk of developing specific sensitization (RR = 4.96, 95% CI = 2.91 to 8.45); atopy (RR = 2.18, 95% CI = 1.22 to 3.88) and respiratory symptoms in the pollen season (RR = 6.46, 95% CI = 1.96 to 21.28) remained significant. All results were adjusted for sex as this variable was associated with the outcome.

DISCUSSION

This prospective study in apprentices exposed to high-molecular-weight occupational allergens shows (1) the greatest number of incident cases were in animal health apprentices, followed by pastry making and then dental hygiene apprentices; (2) a non-negligible number of new cases of sensitization to non-work-related occupational antigens was found in all three programs, although there was a higher proportion of sensitization to agents related to the program in the animal health and dental hygiene programs; (3) in the animal health program, the determinants for the development of program-related sen-

TABLE 4
CUMULATIVE NUMBER OF HOURS SPENT IN CONTACT WITH SPECIFIC ALLERGENS PER SCHOOL BY END OF TRAINING IN EACH PROGRAM

Program	Schools (n)	Specific Allergens	Cumulative [‡] Duration of Exposure per School (h)		Time [§] to Reach Maximal Duration (mo)
Animal health	5	Rodents* (rat, mice, and rabbit)	Median	48.1	
			School no. 1	74	28
			School no. 2	48	28
			School no. 3	52	28
			School no. 4	38	28
			School no. 5	16	20
Pastry-making	7	Flour [†] (wheat, bran, and mixed)	Median	1,116.0	
			Min	1,020	16
			Max	1,173	16
Dental hygiene	2	Latex [†]	Median	517.5	
			Min	497	32
			Max	538	32

* Set of specific allergens defined *a posteriori* (i.e., excluding guinea-pig dander and hamster dander (see Table 2).

[†] Set of specific allergens defined *a priori* (see Table 2).

[‡] Cumulative hours of exposure are presented here; however, in Cox regression analyses, time to the event was used as the time-dependent variable.

[§] Time after entry in the program.

TABLE 5
EFFECTS OF HOST AND ENVIRONMENTAL FACTORS ON THE
INCIDENCE OF SPECIFIC SENSITIZATION BY TRAINING PROGRAM*

	No. of Subjects with Characteristic		RR	95% CI
	All	Cases		
Animal health [†] , n	382	85		
Atopy	144	58	3.5	2.1–5.6
Hay fever	25	12	3.1	1.5–6.2
Asthma	34	13	2.3	1.2–4.4
Exercise-induced respiratory symptoms	75	30	2.4	1.5–3.9
Cold-air-induced respiratory symptoms	55	22	2.6	1.5–4.4
Rhinitis on contact with pets	106	44	2.7	1.7–4.3
Respiratory symptoms on contact with pets	21	9	2.1	0.89–4.8
Respiratory symptoms in the pollen season	11	8	7.2	3.1–16.8
Immediate skin reaction to pets	60	32	3.4	2.1–5.6
Exposure to rodents, h				
≤ 16	128		1	—
17 to ≤ 52	164		1.0	0.56–1.79
> 52	87		2.05	1.11–3.78
School [§]				
No. 1	115	36	6.7	3.3–13.7
No. 2	31	4	1.4	0.39–4.8
No. 3	84	15	2.4	1.1–5.5
No. 4	61	13	2.6	1.1–6.1
No. 5	105	17	1	—
School 1 versus other schools	115	36	3.9	2.4–6.5
Pastry-making, [‡] n	176	8		
Atopy	77	6	4.0	0.8–20.7
Hay fever	22	4	10.4	2.3–46.6
Father with asthma	9	3	5.9	1.1–30.2
Immediate skin reaction to grass pollen	54	4	6.4	1.2–32.8
Dental hygiene, [‡] n	110	7		
Atopy	47	7	Undefined	p < 0.01
Asthma	10	3	8.9	2.0–39.8

* Rate ratios (RR) and 95% confidence intervals (CI) estimated by univariate Cox regression analyses.

[†] Incident cases of specific sensitization to program-related allergens according to the *a posteriori* definition (i.e., excluding guinea-pig dander and hamster dander; see Table 2).

[‡] Incident cases according to the *a priori* definition in the pastry-making program and the dental hygiene program (i.e., including wheat, bran, and mixed flours; see Table 2).

[§] ≤ 16 h of exposure is the reference category.

^{||} p Value in Fisher exact test.

sitization included atopy, rhinitis on contact with pets, immediate skin reaction to pets, respiratory symptoms in the pollen season, and either school attended or the number of hours spent in contact with rodents.

Most epidemiologic studies carried out in workforces exposed to laboratory animals have been of the cross-sectional type. Newman-Taylor and Gordon (15) reported prevalence proportions of laboratory-animal allergy in the order of 20 to 40% and of occupational asthma of approximately 10%. Cullinan and coworkers (16) studied the occurrence of work-related symptoms in a cohort of 238 workers in three institutions specializing in small-animal research who had not been exposed to laboratory rats before their current employment. These symptoms were related to exposure intensity. The relationship was stronger in atopic subjects but unrelated to smoking. However, no data were available on the immunologic-atopic status of these workers at the time they started employment in these particular sites. Most studies of bakers' allergy or asthma have been cross-sectional. The first prospective study of baker apprentices to investigate the development of skin sensitivity to bakers' allergens and skin, nose, and chest symptoms was done in Germany on a group of 678 subjects (17). In the initial phase of their cohort study, which included 264 workers exposed to flour without previous occupational exposure to flour but with a median duration of employment of 26 mo at the

site, Cullinan and coworkers (18) found that the occurrence of new work-related symptoms was related to intensity of exposure; sensitization was related to exposure intensity, but the relation was confounded by atopy. Among workers in a surgical glove manufacturing plant investigated in a cross-sectional study, 11% (7/64) had skin reactivity to latex and 6% (3/50) had occupational asthma (19). A similar study carried out in nurses exposed to latex showed prevalence figures of 5% for skin reactivity and 2.5% for occupational asthma (8). Sussman and coworkers found an incidence of latex sensitization of 1% in 435 health-care workers followed prospectively for 1 yr who had negative skin test to latex at the first assessment (20). These workers had nevertheless been exposed for many years at the time of first assessment.

Two findings of our study point to the relevance of conducting a prospective study in a group of subjects not previously exposed to work-related allergens during the course of an apprenticeship or a job. First, the fact that 8.6% of apprentices (n = 59) were sensitized to an allergen relevant to the program when they started their studies illustrates the importance of observing subjects not previously exposed, as the first assessment took place within 3 mo after starting apprenticeship (mean 1.4 mo ± 1.5) when no or very limited exposure takes place. All of these subjects were either in the animal health (n = 49) or in pastry-making (n = 10) programs. As

TABLE 6
EFFECTS OF HOST AND ENVIRONMENTAL FACTORS ON
THE INCIDENCE OF SPECIFIC SENSITIZATION[†]
IN THE ANIMAL HEALTH PROGRAM*

	No. of Subjects with Characteristic		RR	95% CI
	All	Cases		
n	382	85		
Atopy	144	58	2.20	1.24–3.91
Hay fever	25	12	1.87	0.82–4.26
Asthma	34	13	0.54	0.20–1.44
Exercise-induced respiratory symptoms	75	30	1.72	0.82–3.62
Cold-air-induced respiratory symptoms	55	22	0.99	0.41–2.40
Rhinitis on contact with pets	106	44	1.57	0.90–2.75
Respiratory symptoms on contact with pets	21	9	0.46	0.16–1.27
Respiratory symptoms in the pollen season	11	8	5.19	1.68–16.05
Immediate skin reaction to pets	60	32	1.60	0.82–3.11
Exposure to rodents, h				
≤ 16 [‡]	128		1	—
17 to ≤ 52	164		1.0	0.54–1.85
> 52	87		2.51	1.32–4.76

* RR and 95% CI estimated by multivariate Cox regression analysis.

[†] Incident cases of specific sensitization to program-related allergens according to the *a posteriori* definition (see Table 2).

[‡] ≤ 16 h of exposure is the reference category.

mentioned in the initial description of this cohort, we suspect that the presence of IgE-mediated immunologic reactivity on entry can be explained by specific work-related allergens cross-reacting with common inhalants (work-related laboratory animals and pets, flour, and grass pollen) (11); we cannot exclude that it could be due to some exposure to program-specific allergens, although it is unlikely. Making the assumption that these sensitized subjects were not sensitized on entry would have significantly and wrongly increased the frequency of sensitization attributable to new exposure. These findings further highlight the importance of including subjects not previously exposed (21). Furthermore, taking a longitudinal approach in young apprentices starting exposure made it possible to limit the influence of other environmental factors (22).

Second, conducting the study in three different apprenticeship programs in which students were exposed to high-molecular-weight allergens provided us comparison groups for each of the targeted programs. Many subjects acquired sensitization to allergens that were, theoretically, absent from their apprenticeship milieu (Table 2); however, incident sensitization to latex among students in the animal health program can be explained by the use of latex gloves when handling animals documented in the questionnaire. The fact that these students became sensitized to allergens not present in their own program can be explained by one of two possibilities: either they were exposed elsewhere in their lives, directly or indirectly, or these milieu-specific antigens cross-react with common inhalants. However, there was clearly an excess of incident sensitization to animal-derived allergens in the animal health program and to latex in the dental hygiene program, which would seem to indicate that studying in these programs is indeed a risk factor for sensitization to these agents.

The incidence rate of sensitization in the three programs for which the maximal duration of exposure was 44 mo was highest among animal health apprentices, followed by pastry-making and then dental hygiene students. Because the baseline characteristics of the apprentices starting exposure were similar in the three programs, we can reasonably hypothesize that

the nature of the allergen or the environmental characteristics, or both, are crucial in the likelihood of becoming sensitized.

In the case of apprentices in the pastry-making program, we found that the risk of sensitization to flour was not significantly different than in the other two groups presumed to reflect the exposure to flour in a similar but occupationally unexposed population. We therefore proposed the distinction of an *a priori* definition (suspected increased risk) from an *a posteriori* definition (confirmed increased risk) of cases in the analysis of results. We want to stress that these results apply to exposure to flour in apprentices enrolled in a program of a maximal duration of 18 mo but cannot be extrapolated to subjects with a longer duration of work-related exposure. These results do suggest, however, that the time-course of sensitization differs depending on the nature of the aeroallergen.

Higher prevalence of specific sensitization has generally been shown in workers exposed to animal-derived allergens (in the order of 20 to 40%) (15) as compared with flour (in the order of 5 to 25%) (23) and latex (in the order of 5%) (8, 10). Finally, within the animal health program, incident cases of sensitization accounted for approximately three times the number of prevalent cases at entry for rabbit dander, guinea-pig dander, rabbit urine, and mouse urine (Table 2). However, this ratio was 62/14 (4.4) in the case of rat urine. Gordon and coworkers found that urine is the major source of allergens for rats and mice, and that the allergenic proteins appear in the urine, particularly of male animals after puberty, and disappear after castration; in addition, they found that male rats develop chronic renal disease and secrete increasing concentrations of serum albumin as they mature (24). Heederik and coworkers have demonstrated exposure-response relationships for work-related sensitization in workers exposed to rat urinary allergens (13). Taken together, all these findings suggest that the nature of the allergen is crucial to the likelihood of developing sensitization. Although we previously showed that the concentration of airborne allergens assessed by immunologic methods was much higher in pastry apprenticeship schools than in animal health and dental hygiene schools (25), for a specific antigen, the concentration of allergens also plays a crucial role. In the animal health program, we showed that the number of hours spent in contact with rodents was a determinant of sensitization. Although we did not directly assess the concentration of antigens, it has been shown that the number of hours spent in contact with an allergen can be used satisfactorily as a surrogate for direct assessment of allergens (13).

Atopy was shown to be highly significantly associated with incidence of specific sensitization in the animal health program (Table 6), a fact that has been well documented in many studies reviewed elsewhere (15). Although the power of the analysis was low in dental hygiene and pastry-making programs and the number of cases fewer than 10, our data suggest that atopy was also associated with specific sensitization to latex and to a borderline extent in pastry-making. Atopy has generally been found to be associated with sensitization to flour (23). Sensitization to latex is also associated with atopy, although the predictive value of atopy is only approximately 10% (9). The prevalence of atopy in the three groups was 40.4% to 47.7%, which compares with recently reported prevalence figures in young adult populations varying from 35% to 58% (26–29). Interestingly, reporting rhinitis symptoms on contact with pets before starting apprenticeship was also associated with incidence of sensitization in the case of animal health apprentices. This association has been suggested in a recent cross-sectional study (5). Also of interest, hay fever on entry into the program was strongly associated with the risk of sensitization to flour in the pastry-making program. Crossed

immunologic sensitization to grass and wheat-derived allergens is a well-known phenomenon (30). We cannot speculate on the association between upper and lower airway symptoms in the pollen season and the risk for sensitization to laboratory-animal-derived allergens; the latter remained significant after adjusting for other covariates. Finally, reporting asthma on entry into the program was related to the probability of developing specific sensitization in the dental hygiene program.

This study explored some of the determinants of IgE-mediated sensitization to proteinic allergens, which is the initial step in the natural history of occupational asthma caused by high-molecular-weight agents (31). Our findings are also relevant to the natural history of IgE-mediated asthma caused by protein-derived allergens.

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