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Respiratory symptoms and airway responsiveness in apparently healthy workers exposed to flour dust

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Respiratory symptoms and airway responsiveness in apparently healthy workers exposed to flour dust. A.B. Bohadana, N. Massin, P. Wild, M-N. Kolopp, J-P. Toamain. ©ERS Journals Ltd 1994.

ABSTRACT: Our aim was to measure the levels of exposure to wheat flour dust in a modern industrial bakery, and to assess the relationship between respiratory symptoms, sensitization to wheat flour antigens and airway responsiveness in the workforce.

Forty four flour-exposed male workers and 164 unexposed controls were examined. Inspirable dust concentrations were measured using personal samplers. Respiratory symptoms were assessed by questionnaire, sensitization to wheat flour antigens by skin-prick tests, and methacholine airway challenge (MAC) test using an abbreviated method. Subjects were labelled MAC+ if forced expiratory volume in one second (FEV_1) fell by 20% or more. The linear dose-response slope (DRS) was calculated as the percentage fall in FEV_1 at last dose divided by the total dose administered.

Inspirable dust concentrations were within acceptable limits in all working areas but one. The proportion of subjects with one or more symptoms and with airway hyperresponsiveness was significantly greater among flour-exposed workers than among controls. Using logistic or linear regression analysis, airway responsiveness was found to be strongly related to working at the bakery and to the baseline level of lung function. A positive skin-prick test was found in only 11% of flour-exposed workers and 6% of controls.

In conclusion, our data show that despite exposure to relatively low concentration levels of inspirable flour dust, subjects working in the baking industry are at risk of developing both respiratory symptoms and airway hyperresponsiveness.
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Individuals working in dusty environments face the risk of inhaling particulate materials that may lead to adverse respiratory effects. In the baking industry, exposure to wheat flour dust may cause respiratory illness of varying nature and severity, ranging from simple irritant symptoms to allergic rhinitis or occupational asthma [1]. Potential allergens implicated are the components of wheat flour itself, flour contaminants, such as mites, weevils and moulds, or flour additives, especially yeast and Aspergillus derived amylase [2–4]. Sensitization to one or more such allergens may result in increased prevalence of respiratory symptoms and airway hyperresponsiveness [5, 6]. As a consequence of flour exposure, however, workers who develop sensitivity to common allergens may selectively drop out of the industry [6]. If such self-selection takes place systematically in the baking industry, it is reasonable to expect workers who stay in the job to be less atopic and, consequently, relatively free of atopic-related symptoms and airway hyperresponsiveness. Such expectation seems even more justified if one considers that modern engineering systems are now available which limit air pollution of modern bakeries, thus contributing to decreasing the intensity of flour dust exposure and, hence, sensitization to flour antigens.

The present study was carried out to measure the levels of exposure to wheat flour dust in a modern industrial French bakery, and to determine the prevalence of upper and lower respiratory tract symptoms and sensitization to wheat flour allergens in the apparently healthy workforce. Additionally, we also attempted to better understand how the above variables relate to airway responsiveness to methacholine. The results were compared with those obtained in a relatively large group of unexposed control subjects.

Materials and methods

Study design and population

The study was a cross-sectional survey of male employees, comprising the workforce at an industrial bakery in

Table 1. – Anthropometric characteristics and smoking habits of flour-exposed workers and controls

Parameter	Flour-exposed n=44	Controls n=164
Age yrs	35±11	38±09
Height cm	175±08	175±06
Weight kg	74±13	76±10
Work duration yrs	8±07	15±11
Smoking history		
Smokers n (% of total)	25 (57)	84 (51)
Tobacco cons. pack-years	10±8	15±12
Ex-smokers n (% of total)	7 (16)	41 (25)
Tobacco cons. pack-years	17±11	14±11
Nonsmokers n (% of total)	12 (27)	39 (24)

Results are given as mean±SD except where indicated. Cons: consumption.

Strasbourg, France; of the 52 current employees, 44 were studied. The control population was a group of 164 males, who were not clerical staff, and who had never been at occupational risk of exposure to wheat flour dust or any other respiratory hazard. They represented 95% of the workforce (n=173) at the following manufacturing plants: 1) electrical engineering (n=6); 2) salt-packing factory (n=40); 3) food distribution (n=27); 4) stationery factory (n=27); 5) glass shop (n=55); and 6) miscellaneous (n=9). The latter group comprised 2 electrical mechanics, 4 caterers, 2 salesmen and 1 business manager. Information was obtained concerning age, working hours per day, duration of work and occupational history. The prestudy characteristics of the flour-exposed workers and controls are shown in table 1.

Air sampling and exposure ranking

Concentrations of airborne dust in the working areas were determined with personal air samplers. Closed-face filter holders were used (Millipore, Massachusetts, USA), housing preweighed 37 mm diameter glass microfibre filters (GF/C, Whatman), connected to portable, battery operated vacuum pumps, sampling at airflow rates of 1 $l \cdot min^{-1}$. The average inhalable particulate concentration was determined from the increase in filter mass (Mettler M3 microbalance) and rates and duration of airflow.

The bakery was divided into five areas, according to job assignment, and, within each area, 2–6 personal samples were taken over 4 h periods (range=3–6 h). For a given area, the average dust concentration was calculated as the mean value of the measurements obtained in that area: the figures were rounded to the nearest whole number to provide a dust score which was assigned individually to all workers in the area. Next, for a given worker, the dust score was multiplied by the number of working months in the area, either for the period of employment as a whole or for the last 5 yrs of employment only. This allowed for the calculation of two indices of estimated dust exposure, namely the total cumulative dust exposure and the cumulative dust exposure in the last 5 yrs.

Medical history and clinical examination

Subjects were defined as "apparently healthy", as none spontaneously reported complaints in the previous few months. Detailed histories concerning chest diseases and smoking habits were recorded. All subjects completed a modified version of the European Coal and Steel Community questionnaire on respiratory symptoms, which was administered by the same experienced interviewer [7]. The questionnaire emphasized the past and present personal and family histories of chronic bronchitis, cough, asthma, wheezing, dyspnoea, nasal symptoms, urticaria and eczema. Chronic bronchitis was defined as cough and phlegm for at least 3 months each year for not less than 2 successive years. The term cough and phlegm was used to define those subjects whose cough and/or phlegm did not fulfil the criteria for chronic bronchitis. Dyspnoea on exertion was considered to be present when the subjects complained of breathlessness while walking up a slight hill. Several questions were asked to assess asthma and eczema; for the purpose of this study, however, we considered these conditions to be present only if the subject answered affirmatively to the question: "Have you ever been diagnosed as having bronchial asthma (or eczema)?".

Nonsmokers were defined as subjects who had never regularly smoked one or more cigarettes a day, or had smoked one or more cigarettes for less than one year. Current smokers were subjects who reported regular smoking of one or more cigarettes a day for at least one year. Ex-smokers were subjects who reported smoking one or more cigarettes a day regularly in the past but who had quit smoking at least one year prior to the study.

Pulmonary function tests

Spirometry was carried out using an electronic thermistance spirometer (Fukuda ST 300, Tokyo, Japan). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and maximal expiratory flows at various lung volumes were obtained by having the subject expire forcefully after a maximal inspiratory manoeuvre. At baseline, each subject performed at least three reproducible forced expiratory manoeuvres (within 5% for FVC and FEV_1); thereafter, only two reproducible curves were required. The curve exhibiting the highest sum of FEV_1 plus FVC was retained for analysis. The results were expressed as a percentage of the predicted values of the European Steel and Coal Community [8].

Airway responsiveness

Since the examinations were carried out during working hours at the bakery, an abbreviated version of the methacholine airway challenge (MAC) test was used [9]. Three cumulative doses of a methacholine solution (0.5, 2.5 and 7.5 µmol) were administered, using a nebulizer (Mediprom FDC 88, Paris, France) delivering doses of 0.5 µmol of methacholine per breath. A noseclip was worn, and the aerosol inhaled through the mouth by slow inspiratory capacity manoeuvres, each followed by a 5 s breathhold. Spirometry was performed in the sitting position, before and 3 min after the aerosols of methacholine. The challenge test was discontinued either after the inhalation of the third dose of methacholine or if the FEV_1 fell by 20% or more below the baseline value.

Subjects who experienced a fall in FEV_1 of 20% or greater were classified as having a positive MAC test (MAC+), *i.e.* airway hyperresponsiveness. A linear dose-response slope (DRS) was calculated by the method proposed by O'CONNOR *et al.* [10], as the percentage fall in FEV_1 at last dose divided by the total dose of methacholine administered.

Skin tests

The wheat flour extract for skin-prick test was prepared by Stallergenes Laboratories, Fresnes, France. Briefly, 1 gm of wheat flour used in the bakery was defatted and, after repeated centrifugation, the supernatant solution was dialysed against distilled water and against normal saline; the final filtered protein concentration of the solution was 10 mg of protein·ml^{-1}. The forearm of the subject was thoroughly cleaned and a drop of the flour extract was applied. The skin was pricked with a needle and excess antigen wiped off. A 9% codeine phosphate solution was used as a positive control and the 50% glycerinated diluent as a negative control. A positive skin test was defined as the presence of a wheal reaction the diameter of which was larger than half that of the positive control.

Ethics

The study was approved by the "Comité Consultatif de Protection des Personnes participant à la Recherche Bio-Médicale" of the Meurthe-et-Moselle County.

Statistics

Statistical analysis was performed using the SAS statistical software. Because many subjects had an FEV_1 that remained stable or improved slightly during the methacholine challenge, which resulted in zero or negative value, a constant had to be added to all DRS values in view of a logarithmic transformation. Thus, we tested the populations by the Shapiro-Wilk test [11], in order to find out the constant yielding a distribution as close to normal as possible. The best results were found when DRS was expressed as 1/(slope+2.5). For controls, this resulted in a fairly normal distribution (p=0.842); whereas, for the flour-exposed group (p=0.153), a skewed distribution was found, with a greater proportion of subjects with low DRS values than in the control group. It should be stressed, however, that no other method, including logarithmic transformation, produced a normal distribution for the exposed group.

Comparisons of categorical variables were performed using the Chi-squared test or, when the expected cell counts were less than 5, the Fisher's exact test. The significance of the relation of potential explanatory variables to symptoms and bronchial reactivity was assessed by logistic regression analysis. For continuous variables, t-tests and linear regression analysis were used. The explanatory variables included: age, sex, smoking category, tobacco consumption in pack-years, whether the subject had ever worked at the industrial bakery, duration of exposure taken as duration of employment in the bakery, dust exposure, total cumulated dust exposure, and dust exposure in the last 5 yrs.

Results

Dust exposure

Mean inspirable dust concentrations well below 10 mg·m^{-3} were observed in all sections of the bakery, except in those related to special bread baking procedures, where much higher values were found in all samples tested (table 2).

Respiratory symptoms, baseline level of lung function and skin tests

Analysis by symptom did not show a statistically significant greater prevalence of chronic cough and/or phlegm, wheezing, dyspnoea, running nose and urticaria

Table 2. – Inspirable dust concentrations according to job assignment in the bakery

Worker's category	Workers n	Samples n	Inspirable particulate mass mg·m^{-3}		Rank
Deliverymen	6	0	–	–	0
Croissant maker	7	4	0.69±0.17	(0.54–0.85)	1
Oven handler	5	6	1.11±0.87	(0.45–2.73)	2
Frozen dough handler	8	2	2.13	(1.89–2.37)	3
General baker	14*	4	3.37±3.66	(0.66–8.70)	4
Special baker	4	5	41.3±39.5	(10.1–98.1)	5
Total	44	21	–	–	–

Data are presented as mean±SD, and range in parenthesis. *: including one polyvalent (multi-functional job) and one maintenance staff.

Table 3. – Respiratory symptoms and baseline pulmonary function tests (PFTs) among flour-exposed workers and controls

	Flour-exposed n=44	Controls n=164	p-values for differences
Symptoms			
Chronic bronchitis	2	2	–°
Chronic cough/phlegm	10	24	0.249
Asthma	1	7	–°
Wheezing	9	25	0.406
Dyspnoea	8	26	0.710
Running nose	8	27	0.720
Eczema	2	16	–°
Urticaria	10	26	0.284
One or more symptom (%)	26 (59%)	57 (35%)	0.0004
Baseline PFTs (mean±SD)			
FVC % pred	96±16	100±11	0.034°°
FEV_1 % pred	95±16	100±14	0.019°°
FEV_1/FVC*	82±06	82±07	0.676
$\dot{V}max_{50}$ % pred	93±28	101±29	0.039°°
$\dot{V}max_{25}$ % pred	85±31	85±31	0.635°°

FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; $\dot{V}max_{50}$: maximal expiratory flow at 50% of the FVC; $\dot{V}max_{25}$: maximal expiratory flow at 25% of the FVC. *: observed value; °: not performed because of the small number of subjects involved; °°: after adjusting for tobacco consumption.

in flour-exposed workers than in controls (table 3). The only flour-exposed worker with reported asthma had developed asthma after entering the baking industry. The proportion of subjects complaining of one or more symptoms was significantly greater among flour exposed workers than among controls (table 3).

Whenever possible, the relationship between individual symptoms and either smoking habits or whether working at the bakery was assessed. Overall, no significant results were found whatever the symptom considered. The best p-values were found for the comparison involving cough and/or phlegm *versus* smoking category (p=0.179), and cough and/or phlegm *versus* whether working at the bakery (p=0.249).

The logistic regression analysis showed that, after adjustment for age and tobacco consumption, symptoms were not significantly related to indices of dust exposure. The highest increase in odds ratio was 1.62 (regression coefficient estimate=0.483, SE=0.426; p=0.258), found for cough and/or phlegm against whether working at the bakery or not.

Table 4. – Airway hyperresponsiveness in flour-exposed workers and controls

Parameter		Flour-exposed n=44	Controls n=164	p-value
MAC+	%	25	7	0.002
	n	11	12	
DRS (1/slope+2.5)				
	Mean	0.25	0.30	
	±SD	±0.09	±0.007	0.0001

MAC+: methacholine airway challenge test positive by spirometry (fell in FEV_1 by 20% or more); DRS: dose-response slope; FEV_1: forced expiratory volume in one second.

After adjustment for tobacco consumption, flour-exposed workers displayed significantly lower baseline level of pulmonary function than did controls (table 3).

A positive skin test to cereal flour antigen was found in 5 out of 44 flour exposed workers (11%), and in 7 out of 118 controls (6%); this difference was not significant (p=0.310).

Airway responsiveness

A positive MAC test (MAC+=FEV_1 fall of 20% or greater) was observed in 23 of the 208 subjects tested. The proportion was almost four times as great among flour-exposed workers as among controls, a statistically significant difference (table 4). Similarly, mean DRS values were significantly lower among flour-exposed workers than among controls, thus indicating an overall increased airway responsiveness in the former group (table 4). For the group as a whole, no significant relationship was found between each index of airway responsiveness and either smoking habits or symptoms. The best p-value was 0.073, observed for the relationship between MAC+ and smoking category.

Logistic regression analysis was used to assess the relationship of explanatory variables to MAC+: after adjustment for tobacco consumption, a significant relationship emerged between this index and working at the bakery, with an odds ratio of 4.76 (regression coefficient estimate=1.560, SE=0.478; p=0.001). After further adjustment for baseline FEV_1, the exposure odds ratio dropped to 3.75 but remained statistically significant (regression coefficient estimate=1.322, SE=0.512; p=0.01). However, no significant relationship was found between MAC+ and estimated indices of cumulative exposure.

Subjects MAC+ were found to have significantly lower values of baseline pulmonary function parameters than subjects MAC-, both among flour-exposed workers and controls (table 5).

Multiple regression analysis was used to assess the relative contribution of measured variables to DRS values.

Table 5. – Baseline level of lung function tests in flour-exposed workers and controls with and without a positive methacholine airway challenge test (MAC+)

Parameter	Flour-exposed MAC+ n=11	Flour-exposed MAC- n=33	p-value
FVC % pred	83±15	99±14	0.042
FEV_1 % pred	87±21	99±13	0.002
$\dot{V}max_{50}$ % pred	67±17	102±26	0.0001
$\dot{V}max_{25}$ % pred	64±18	92±31	0.006
Parameter	**Controls MAC+ n=12**	**Controls MAC- n=152**	**p-value**
FVC % pred	96±11	100±13	0.281
FEV_1 % pred	89±14	100±11	0.005
$\dot{V}max_{50}$ %pred	74±22	104±29	0.0005
$\dot{V}max_{25}$ % pred	57±22	87±30	0.0008

Data are presented as mean±SD. For abbreviations see legend to table 3.

Table 6. – Multiple regression of the dose-response slope (DRS=1/[% fall FEV_1/μmol+2.5]) on baseline FEV_1 (obs/pred), age (years) and exposure to flour dust expressed either as a categorical variable (upper section) or in terms of years of exposure*

Factor	Coefficient	SE	p-value
Constant	0.0164		
Baseline FEV_1	0.2151	0.0357	0.0001
Age	0.0009	0.0005	0.0777
Never exposed	0.0381	0.0120	0.0018
r^2	0.21		
Constant	0.0394		
Baseline FEV_1	0.2094	0.0358	0.0001
Age	0.0014	0.0005	0.0058
Duration of exposure*	-0.0038	0.0011	0.0008
r^2	0.22		

FEV_1: forced expiratory volume in one second.

Smoking habits, cumulated dust exposure, results of the skin tests and the number of symptoms were dropped from the model after they were found to have a non-significant relation to DRS (p-values between 0.3497 and 0.681). The only variables likely to influence DRS values were dust exposure, taken either as a categorical variable or expressed in terms of duration of exposure in years, and baseline FEV_1. The significance of the values included in this model for the group as a whole is shown in table 6. From the model it can be calculated that a 40 year old flour-exposed worker, whose ratio of observed over predicted baseline FEV_1 is 0.7, would have a DRS of 0.20; whereas, an unexposed control of identical age and baseline FEV_1 would have a DRS of 0.24.

Discussion

In France, at present, no specific recommendations exist regarding the threshold limit value for flour dust exposure. Compared to the 10 mg·m^{-3} exposure threshold for nuisance dust [12], the mean inspirable dust concentrations that we observed were within acceptable limits in all production areas of this bakery, except the special bread baking area, where exceedingly high values were noticed. The area-to-area variability of dust concentration measurements was large: for a given area, the highest over lowest concentration ratio varied between 1.25 (frozen dough handling area) to 13 (general baking area) (table 2). A great variability of flour dust concentration in bakeries has been reported previously [5], and seems to be a frequent condition when dealing with dust in general [13]. In the setting of this study, it could be explained on the basis of the variability of flour dust emanating from the baking process itself, the movements of the worker close to and away from the baking process, and the effects of external factors, such as ventilation near the baking process. Additionally, it could also have been influenced by resuspension of dust from clothing, a finding described when using personal dust samplers [14].

This study showed that the proportion of subjects who complained of one or more upper and/or lower respiratory symptoms was significantly greater among flour-exposed workers than among control subjects (table 3). When we compared the prevalence of symptoms of our flour-exposed group with that of previous studies from the literature, agreements and disagreements arose according to the symptom considered. For instance, for chronic bronchitis, our observed 5% prevalence rate was slightly lower than the 8% found in 2,191 bakers in Paris [15]; lower than the 13% observed in 279 British bakers [5]; and much lower than the 25% reported in 176 Australian bakers [6]. Conversely, for wheeze, our observed 20% value was identical to the value reported in the Australian study [6]; whereas, for dyspnoea, our 18% value was only slightly greater than the 14% found among British bakers [5]. Although they are interesting, such comparisons should be interpreted cautiously, because the above studies differed from one another in many respects, for instance, the sample size, the methodology of data collection and the mode of expressing the results.

Much more striking were differences related to abnormalities of airway responsiveness: flour exposed workers displayed a significantly greater prevalence of positive MAC tests and a significantly steeper dose-response slope (DRS) than did controls. If one accepts that airway hyperresponsivenes is a composite physiological disorder, the following parameters at least, could have influenced the above two indices: age, tobacco smoking, allergy, exposure to flour dust and baseline level of lung function.

Previous studies have addressed the relationship between airway responsiveness and age. Some authors have observed an increased histamine responsiveness with age in a random population sample [16]; whereas, others have found similar results among smokers, but not among atopic nonsmokers, whose responsiveness actually decreased with age [17]. In this study, no significant relationship was found between airway responsiveness and age for the group study as a whole, or for the flour-exposed and unexposed groups examined separately, except when the duration of exposure was taken into account (table 6).

Tobacco smoking *per se* may cause airway hyperresponsiveness. In population-based studies, smokers have been found to have an increased responsiveness both to histamine [18], and to methacholine [19]. However, somewhat conflicting results were observed in occupational groups: Enarson *et al.* [20] performed methacholine challenge tests in 504 white male grain-handlers and found hyperresponsiveness to be more frequent among smokers than among nonsmokers, but the differences were not significant. In this study, no relationship was found between the two indices of bronchial responsiveness and smoking habits, either among the population sample as a whole, or among flour-exposed workers and controls examined separately. This finding could have been due, at least partly, to the fact that the cumulative cigarette exposure of our subjects in terms of pack-years might not have been sufficiently high.

The relationship between allergy and bronchial responsiveness has been examined with respect to common allergens and to specific allergens in the workplace. Among population samples chosen without regard to symptoms or medical history, cutaneous reactions to common allergens were found to be associated with higher degrees of nonspecific airway hyperresponsiveness [17, 21]. On the other hand, among occupational samples, exposure to specific antigens in the workplace may lead to occupational asthma and airway hyperresponsiveness [22], which may either persist [22], or diminish after exposure to the relevant antigen is eliminated [23]. In this study, the flour-exposed group showed a relatively low prevalence of positive skin tests against wheat flour antigens, a finding similar to that reported previously in bakers [6]; this observation is compatible with self-selection due to the well-known "healthy worker effect" [24].

The importance of the atopic status as a factor in job decision-making in flour-exposed workers has been further documented by Dosman *et al*. [25]. These authors skin tested cereal grain workers and control subjects with a battery of 14 allergens, including wheat dust extract, within the first months of their employment and again 1.3 yrs later. At the second examination, the percentage of control subjects with a positive test had reduced slightly (from 33 to 25%), whereas that of grain workers had declined sharply (from 25 to 8%), a finding explained by the fact that workers with positive skin tests had dropped out of the industry, probably because of respiratory symptoms. As we have not skin tested our populations longitudinally, we cannot, of course, demonstrate that selection has really occurred among them.

A positive relationship between responsiveness to methacholine and exposure to flour dust has been reported before. Prichard *et al*. [6], found a provocative dose producing a 20% fall in FEV_1 (PD_{20}) <30 μmol in 41% of bakers (n=176) but in only 21% of controls (n=24). Musk *et al*. [5] showed the proportion of bakers with a PD_{20} <30 μmol to increase from 26% in those less exposed to 42% in those more exposed. In this study, we observed a significant dose-response with the duration of exposure, but not with indices of cumulated dust exposure, a finding consistent with the hypothesis that bronchial hyperresponsiveness may result from longstanding low level dust exposure.

A significant relationship between airway hyperresponsiveness and low baseline level of lung function has been shown in subjects from the general population [18, 19, 26], as well as in subjects with chronic mucus hypersecretion [27–29]; in confirmed asthma more conflicting results were reported [30–33]. Apart from anatomical and airway geometric factors [34], the association between airway hyperresponsiveness and low baseline level of lung function could be explained by the fact that both are manifestations of chronic airway inflammation. However, had it been present in our flour-exposed group, the latter abnormality *per se* could not be taken as a proof that the observed bronchial hyperresponsiveness was just a consequence of the low baseline level of lung function.

Despite the importance of the aforementioned factors, it should be noted that their contribution to explaining the variability of indices of airway responsiveness is relatively low. In this study, flour dust exposure (or duration of exposure) and baseline level of pulmonary function taken together explained only 21% (or 22%) of the variability of DRS. This finding reinforces the idea that airway responsiveness may be determined by several factors, some of which are probably still unknown.

In conclusion, this study showed that despite exposure to relatively low concentration levels of inspirable flour dust, otherwise healthy subjects working in the baking industry had a significantly greater number of symptoms and of abnormalities of airway responsiveness than did unexposed control subjects. This observation highlights the importance of hygiene measures aimed at improving the air quality in the workplace.

Finally, the detection of airway hyperresponsiveness in apparently healthy workers exposed to occupational hazards is important in the light of the theory that this abnormality might carry the risk of developing irreversible airflow obstruction [35, 36]. In order to better examine the nature of the findings reported here, a longitudinal survey of the respiratory health status of this occupational sample is currently being planned.

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