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Respiratory symptoms and pulmonary function of workers exposed to cork dust, toluene diisocyanate and conidia

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ALEGRE J, MORELL F, COBO E. Respiratory symptoms and pulmonary function of workers exposed to cork dust, toluene diisocyanate and conidia. *Scand J Work Environ Health* 1990;16:175-81. A cross-sectional study on suberosis was conducted to determine the prevalence of respiratory symptoms and the level of pulmonary function, and their relationships within job categories of exposure to cork dust, toluene diisocyanate (TDI) resin bonding and conidia, among cork workers. Exposure-response relationships, with confounders taken into account, showed specific associations between cork dust and chronic bronchitis, TDI and asthma, and conidia and symptoms of hypersensitivity pneumonitis. Workers exposed to these risk factors had reduced mean spirometric values. A significant correlation between a decrease in pulmonary function and length of exposure was found for the workers exposed to cork dust. These results strongly suggest that suberosis, as hitherto described, might in fact be comprised of three different diseases with different etiologic risk factors, ie, respiratory hypersensitivity from exposure to conidia, asthma from exposure to TDI, and chronic obstructive pulmonary disease from exposure cork dust.

Key terms: chronic obstructive pulmonary disease, cross-sectional study, exposure-response relations, respiratory hypersensitivity, suberosis.

Suberosis, a respiratory disease of cork workers, was first described by Portuguese authors (1) as hypersensitivity pneumonitis, and the pathology included sarcoid-type granulomas with cork inclusions in the pulmonary interstitium and bronchial wall (2). The etiology was attributed to cork dust and *Penicillium frequentans* (3, 4), although inhalatory provocation tests were only positive to *P frequentans*. Nevertheless, the clinical presentation of suberosis was polymorphous, since patients complained of symptoms typical of either hypersensitivity pneumonitis or asthma and even a form of bronchitis (2).

Toluene diisocyanate (TDI) is used in the cork industry for the processing of cork agglomerates. Despite the known risk of asthma with exposure to TDI (5-11), its etiologic role in suberosis has not been considered until now. Furthermore, occupational exposure to cork dust in grinding and polishing has not been studied as a possible risk factor for other respiratory diseases.

Taking into account the aforementioned risk factors, we suggest that the varied symptomatology of suberosis may point to several different diseases, each with its own determining factor.

Since few attempts to detect suberosis have been made in Spain, the world's second largest producer of

cork, this study was conducted to determine the prevalence of respiratory symptoms and the level of pulmonary function of Spanish cork workers and to analyze relations between these two factors and occupational exposure in the cork industry.

Subjects and methods

Forty-two small factories involved in various stages of cork processing were surveyed in 1984. From a total of 488 workers the final study group consisted of 442. The 46 nonrespondents included 36 who refused to participate and 10 who were absent for health reasons, although none suffered from respiratory ailments.

Cork manufacturing process

Processes involved in the manufacture of cork depend on the end product to be obtained. "Natural" stoppers (wine-bottle corks) are made from bark which is boiled, stored under dark humid conditions until moldy, sliced, punched, and polished; cork agglomerates for use as parquet flooring, wallpaper, wall coverings, bulletin boards, shoe soles, life belts, champagne corks, etc, are manufactured from ground bark that is blended with TDI resin bonding; blocks and panels for industrial soundproofing are obtained from ground bark which is agglomerated under pressure and heating.

Risk factors

The criteria for exposure to the respiratory risk factors present in the different stages of cork manufac-

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turing were established according to those of Gamble & Spirtas (12). Technicians from the Gerona Department of Health and Work Safety surveyed 42 factories to study cork processing and the respiratory risk factors involved.

The job-exposure categories were defined as follows according to the qualitative direct exposure in the various job activities: (i) exposure to conidia: working or having worked as a slicer or puncher of moldy cork; (ii) exposure to cork dust: having worked for a minimum of two years as a grinder or polisher of cork; (iii) exposure to TDI: working or having worked as a blender of cork sawdust and TDI resin bonding.

The respective nonexposure categories were those of "not working or not having worked" in the aforementioned job activities.

Personal interview

The following three questionnaires were administered by trained interviewers: (i) a modified version of the standard ATS-DLD-1978 respiratory and smoking questionnaire (13); (ii) an exposure and occupational history questionnaire based on the report of the American College of Chest Diseases of San Diego (14); (iii) a questionnaire to assess hypersensitivity pneumonitis, adapted from the criteria of Grant et al (15) for the study of farmer's lung.

Respiratory diseases

The respiratory illnesses studied were defined as follows: (i) chronic bronchitis: cough and phlegm on most days for at least three months a year for two or more consecutive years (16); (ii) asthma: history of acute, reversible attacks of dyspnea or shortness of breath with wheezing (17, 18); (iii) symptoms hypersensitivity pneumonitis: more than two bouts of occupationally related coughing, chest tightness, or dyspnea without wheezing with or without fever and the cessation of symptoms during exposure-free periods or once exposure has ended.

Pulmonary function

Spirometry was performed with a Vitalograph[®] spirometer (7 l) in a room with a constant temperature according to the instructions of the American Thoracic Society (19) for both the spirometric test and the calibration. Calibrations of the spirometer with an explosive decompressor (20) showed reproducibility within the standards of the American Thoracic Society. The 18 subjects who failed to meet the spirometric requirements were excluded.

Precipitin test

Precipitating antibodies were detected by counter electrophoresis. *P. frequentans* extracts at concentrations

of 10 and 5 mg/ml were used (Ifidesa Aristegui Laboratories, Bilbao, Spain).

Confounding factors

Potential confounders were sex, age, smoking, other exposures with respiratory risk, history of respiratory diseases, atopy (prick-test response to common allergens considered positive when papules measured 3 mm or more in diameter when compared with papules obtained with isotonic saline).

Two age categories (<40 years or ≥40 years) were used in the respiratory symptoms analysis, whereas age was used as a continuous variable in the pulmonary function analysis.

The health effects of smoking (packs/year and cigarettes/day) were assessed. In the multivariate analyses the smoking categories were current smokers (more than one cigarette per day in a year), nonsmokers, and ex-smokers (stopped smoking at least three months before).

Analysis

The main objective of the study was to analyze for exposure-response relationships, and the strategies proposed by Weiss & Liff (21) for studying multifactorial diseases with a cross-sectional design were applied (22). To avoid the confounding effect of multiple exposure, more common for the mobile workers (those currently employed in more than one job activity), all the workers were included in all the job categories to which they had been exposed. When submitted to analysis, the workers in each job category were compared with the rest of the study population to limit bias caused by multifactorial disease.

The data analysis was carried out with the statistical package for the social sciences and the biomedical package. Potential risk factors, relevant for at least 5 % of the study group, formed part of a first bivariate study with respiratory symptoms. The exposure-response associations underwent multivariate analyses which included the confounders. Thus we applied a loglinear analysis (23) for the study of relations between chronic bronchitis, asthma, and symptoms of hypersensitivity with the suspected risk factors. Coefficients of partial association (24) and the estimated adjusted odds ratio (OR) in loglinear models which included interfactorial associations were used for the significance assessment.

The evaluation of pulmonary function with an analysis of covariance (ANCOVA) and a multiple regression focused on determining the dependence of the spirometric parameters [forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_{1.0}), and forced expiratory flow rate at 25–75 % of the forced vital capacity (FEF_{25–75})] on the risk factors under study, after adjustment for age, sex, height, weight, smoking, and the job-exposure categories.

Results

The physical characteristics and smoking categories of the workers are shown in table 1, and their occupational activities are presented in table 2. There was a clear predominance of men in the activities involving exposure to the risk factors (slicing, polishing, and blending). It is important to note the prevalence (14 %) of mobile workers, the relatively short time of employment in the cork industry, and the high prevalence of male smokers.

Newcomers (one year's employment or less) predominated in the job categories in close contact with the proposed risk factors. There were no significant differences in the smoking habits of the workers in the different exposure categories (table 3).

The prevalence of cough, phlegm, chronic bronchitis, daily wheezing, attacks of asthma, and symptoms of hypersensitivity pneumonitis are shown in table 4 according to the smoking and exposure categories. It can be seen that the workers exposed to cork dust

Table 1. Age, height, years worked, and smoking categories of the workers.

	N	Age (years)		Height (cm)		Years worked		Smoking category		
		Mean	SD	Mean	SD	Mean	SD	Non-smokers (%)	Current smokers (%)	Ex-smokers (%)
Men	247	43	13	168	6	14	12	21	57	22
Women	195	38	14	157	7	12	11	77	20	3
Men + women	442	41	14	163	9	13	11	46	40	14

Table 2. Distribution of the workers by current job activity.

	N	Slicing (%)	Grinding (%)	Selectors (%)	Warehouse (%)	Office (%)	Supervisor (%)	Blender (%)	Mobile worker (%)
Men	247	22	11	4	7	8	10	16	22
Women	195	10	2	72	4	5	—	3	4
Men + women	442	16	7	34	6	7	6	10	14

Table 3. Smoking (frequency, chi-squared not significant) and worker turnover by exposure to conidia, toluene diisocyanate (TDI), and cork dust. (95 % CI = 95 % confidence interval)

Exposure	N	Smoking category			Worker turnover	
		Non-smokers (%)	Current smokers (%)	Ex-smokers (%)	%	95 % CI
Overall	442	46	40	14	9	6.3—11.7
Conidia	100	30	51	19	16	8.8—23.2
TDI	50	20	60	20	28	15.6—40.4
Cork dust	52	31	54	15	12	3.2—20.8

Table 4. Prevalence of cough, phlegm, chronic bronchitis, wheezing, asthma, and symptoms of hypersensitivity pneumonitis by job exposure to conidia, toluene diisocyanate (TDI), and cork dust and by smoking category.

	N	Cough (%)	Phlegm (%)	Chronic bronchitis (%)	Wheeze (%)	Asthma (%)	Symptoms of hypersensitivity pneumonitis (%)
Job-exposure category							
Cork dust	52	48	52	38	10	2	8
TDI	50	44	46	34	22	14	6
Conidia	100	37	33	22	3	3	17
Smoking category							
Nonsmoker	203	18	16	10	3	8	8
Smoker	177	50	43	31	10	3	8
Ex-smoker	62	29	38	21	7	8	16
Total	442	32	30	20	6	6	9

(polishers and grinders) had the highest rate of chronic bronchitis (38 %), even higher than that of current smokers (31 %). Similarly, those exposed to TDI (blenders) had the highest prevalence of wheezing (22 %) and attacks of asthma (14 %). Furthermore, this table shows that those workers exposed to conidia (slicers and punchers of moldy cork) suffered the most from symptoms of hypersensitivity pneumonitis (17 %).

The overall prevalence of precipitin positive to *P. frequentans* was 13 %. Twenty-one percent of the workers exposed to moldy cork had positive precipitin ($P < 0.05$). There was no significant relation between symptoms of hypersensitivity pneumonitis and serum precipitins, despite the fact that the subjects with these symptoms had the highest prevalence of positive precipitin (22 %).

To ascertain the role of the confounding factors, primary bivariate analyses were carried out between the confounders and the exposure categories and the respiratory illnesses, respectively. These analyses showed that smoking and sex could cause bias in the study of chronic bronchitis. There was no association between atopy and the exposure categories and the respiratory symptoms.

Chronic bronchitis and exposure to cork dust

The relation between chronic bronchitis and exposure to cork dust was tested in a multivariate loglinear analysis with adjustment for age and smoking. Owing to the small number of women exposed to cork dust, this analysis was restricted to the men.

The coefficients of partial association were statistically significant between chronic bronchitis and exposure to cork dust ($P = 0.022$) and between chronic bronchitis and age ($P = 0.047$). Higher interaction among these three factors was similarly significant ($P = 0.027$). Thus the relationship between cork exposure and chronic bronchitis had a different intensity in the two age groups.

The adjusted odds ratio for chronic bronchitis among the workers exposed to cork dust was 3.44 [95 % confidence interval (95 % CI) 1.48–7.95]. This risk was increased fivefold among the exposed subjects under 40 years of age.

Asthma and exposure to TDI

To ascertain whether the greater proportion of asthmatics among the workers exposed to TDI was related to the TDI exposure, a loglinear analysis was made for attacks of asthma, exposure to TDI, sex, age, and exposure to conidia. The association between asthma and exposure to TDI was significant ($P = 0.01$). The adjusted odds ratio for asthma among the TDI-exposed workers was 3.22 (95 % CI 2.87–3.61).

Symptoms of hypersensitivity and exposure to conidia

To test the association found between symptoms of hypersensitivity pneumonitis and exposure to conidia, an analysis was performed with adjustments for exposure to TDI, sex, and age. The results confirmed a significant relation between symptoms of hypersensitivity pneumonitis and exposure to conidia ($P = 0.0007$) and age ($P = 0.008$). The adjusted odds ratio for symptoms of hypersensitivity among the workers exposed to conidia was 3.23 (95 % CI 1.25–8.33).

Pulmonary function analyses

The effects of the qualitative exposure to the risk factors on the workers' spirometric values were analyzed by ANCOVA. The analysis, summarized in table 5, showed that the exposed subjects had adjusted mean values lower than the overall means. However, only the differences in the $FEV_{1.0}$, as adjusted for exposure-nonexposure with respect to smoking and exposure to conidia, and the differences in the FEF_{25-75} , as adjusted for exposure-nonexposure with respect to smoking and exposure to conidia and cork dust, were significant ($P < 0.05$).

The effects of the duration of exposure to the risk factors on pulmonary function were examined with a multiple regression which tested the relation between each spirometric parameter and the exposure categories, with adjustments for the covariants and smoking. These analyses found only ventilatory impairment with exposure to cork dust and showed a significant correlation between the length of exposure and the adjusted FVC, $FEV_{1.0}$, and FEF_{25-75} means of the workers exposed to cork dust. The adjusted coefficients, which measured the variation of the spirometric parameters in milliliters per year of exposure, are shown in table 6. Smoking had an airflow limitation effect, and current smokers had a higher decrease in $FEV_{1.0}$ and FEF_{25-75} after adjustments for the covariants and exposure categories (table 5).

Discussion

The exposure-response associations between chronic bronchitis and cork dust, asthma and TDI, symptoms of hypersensitivity pneumonitis and conidia, and airflow limitation and exposure to cork dust were the most notable features of this study, which provides additional information on suberosis.

The paucity of information on suberosis in Spain led to the choice of a cross-sectional design for the study, mainly as an initial approach to the problem.

There are three main respiratory risk factors involved in the cork manufacturing process: cork dust in grinding and polishing, conidia in the slicing and punching of moldy cork, and TDI resin bonding in the

blending of cork. Exposure categories, which permitted internal comparison, were established on the basis of the evidence of direct exposure to these risk factors in certain job activities.

Workers' previous illnesses and their occupational profiles were taken into account principally with the objective of avoiding the sources of bias caused by high worker turnover and the healthy worker effect which may confound health assessment (25–27).

The study of prevalences (table 4) suggested exposure-response relationships which were later confirmed in a multivariate analysis. These analyses were always adjusted for sex and smoking.

The first loglinear analysis showed an association between chronic bronchitis and exposure to cork dust, with an odds ratio of 3.44 (95 % CI 1.48–7.95). However, the fivefold increase in the odds ratio of the lower age group of exposed workers could have been due in part to a cessation of exposure and a reduction in smoking in the older age group. This conclusion would be comprehensible if we accept the reversibility of chronic bronchitis symptoms (28–30). These

results support the evidence for industrial bronchitis (31–33) and are coherent with the findings of other studies on exposure to organic dusts such as those of cotton or grain (35–37).

The second loglinear analysis further confirmed the association between asthma and exposure to TDI resin bonding. Enarson et al (18) stated that attacks of dyspnea or shortness of breath with wheezing correlate well with bronchial hyperreactivity and appear useful in epidemiologic research. This is the first time that the aforementioned risk factor has been assessed as a possible producer of asthma in the cork industry. Three arguments in favor of this association were found: (i) the association of asthma only with exposure to TDI (specificity); (ii) the strength of the association (OR 3.22, 95 % CI 2.87–3.61); and (iii) coherence with previous studies on isocyanates (7–9, 38–40). We believe this finding contributes to the understanding of suberosis, since exposure to cork dust or conidia was not significantly associated with asthma in this study.

The relationship between symptoms of hypersensitivity pneumonitis and exposure to conidia was also

Table 5. Analysis of covariance: adjusted^a difference with respect to the grand mean in forced expiration (ml) in the study population by job exposure to conidia, toluene diisocyanate (TDI), and cork dust and by smoking category. (FEV_{1.0} = forced expiratory volume in 1 s, FVC = forced vital capacity, and FEF_{25–75} = mean forced expiratory flow during the middle half of the forced vital capacity)

	N	FEV _{1.0}	FVC	FEF _{25–75}
Job exposure category				
TDI				
Yes	49	–65	–51	–10
No	375	+9	+7	+1
Conidia				
Yes	96	–108	–87	–177
No	328	+32	+25	+52
Cork dust				
Yes	50	–78	–21	–226
No	374	+10	+3	+30
Smoking category				
Nonsmoker	195	+52	+14	+175
Smoker	170	–72	–50	–170
Ex-smoker	59	+35	+98	–90
Total	424	2.957	3.666	2.945

^a Adjusted for age, height, sex, smoking, weight, and job exposure.

Table 6. Multiple regression: regression (β) and determination coefficients (R^2) of the spirometric parameters (dependent variable) with years of job exposure to conidia, toluene diisocyanate, or cork dust (independent variable) after adjustment for age, height, sex, smoking, and weight. (FEV_{1.0} = forced expiratory volume in 1 s, FVC = forced vital capacity, and FEF_{25–75} = mean forced expiratory flow during the middle half of the forced vital capacity)

Exposure	N	FVC		FEV _{1.0}		FEF _{25–75}	
		β	R^2	β	R^2	β	R^2
Cork dust	51	–34.4	–0.13*	–28.5	–0.13*	–40.6	–0.10*
Conidia	97	5.8	0.00	4.3	0.00	1.1	0.00
TDI	49	0.9	0.00	16.4	0.02	42.9	0.04
Overall	427	–0.91	0.00	0.4	0.00	0.4	0.00

* $P < 0.01$.

confirmed by the third loglinear analysis. Those exposed to conidia ran a three times greater risk of symptoms of hypersensitivity pneumonitis. This evidence corroborates the work of Portuguese authors (1–3) who found that the inhalation of *P frequentans* reproduced symptoms of suberosis and that exposure to conidia implies a risk of hypersensitivity pneumonitis (41, 42). Those workers with symptoms of hypersensitivity pneumonitis and fever, the latter persistent with exposure to conidia, also had precipitins to *P frequentans* and restrictive ventilatory impairment, which ruled out the organic dust toxic syndrome (43).

The 95 % confidence intervals of the odds ratios were wide and revealed a certain lack of precision due to the size of the exposure groups after stratification. Another possibility could have led to a lack of precision also. In small industries there is no clear dividing line between exposure and nonexposure. Thus certain subjects with indirect or low levels of exposure may have been included in the nonexposure group (misclassification error). The results on the role of precipitins as an exposure indicator concur with those of other authors (44–46).

The pulmonary function analyses showed the adjusted FEV_{1.0} and FEF_{25–75} means for the subjects exposed to conidia to be significantly lower than those of the unexposed subjects (table 5). Similar results were reported for farmers by Heller et al (47) and Dosman et al (48). A lack of correlation between the spirometric parameters and the length of exposure to conidia may have been due in part to worker turnover, the immunologic nature of hypersensitivity pneumonitis, and a possible tolerance phenomenon in some of the affected subjects (49).

For the workers exposed to cork dust, the ANCOVA found only the mean of the adjusted FEF_{25–75} to be significantly lower than that of the unexposed subjects. On the other hand, the multiple regression (table 6) showed a significant decrease in the spirometric values with length of exposure in that group of workers. This effect may have been due to the airborne character of cork dust (3, 4), and it may point to a dose-response relation. The specificity and significance of this finding, and the increased risk for chronic bronchitis among the workers exposed to cork dust, support the plausibility of an airflow obstruction effect.

We failed to detect any pulmonary function impairment in the TDI-exposed workers. However, this finding may have been due to a selection bias caused either by the high worker turnover or the risk for asthma observed in this group, and by the fact that asthmatic patients have symptom-free periods with normal lung function.

The fact that smoking had a significant airflow limitation effect on pulmonary function in the study population does not explain the aforementioned results with respect to spirometric impairment, which can be attributed to job exposures and inherent risk factors.

Given the plausibility of these associations, follow-up will be necessary.

In summary, exposure to cork dust, TDI, and conidia in cork processing may give rise to symptoms of respiratory disease. Specific exposure-response relationships per exposure category suggest that suberosis is comprised of several different diseases, ie, asthma, chronic bronchitis, and hypersensitivity pneumonitis. Thus, all surveys on suberosis should take into account these factors and diseases. Similarly, surveys on occupational health hazards should consider the fact that the disease under study could be a compound of diverse syndromes caused respectively by different determinants involved in the manufacturing process.

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