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Outbreak of organising pneumonia in textile printing sprayers

*Carmen Moya, Josep M Antó, A J Newman Taylor, and the Collaborative Group for the Study of Toxicity in Textile Aerographic Factories**

Summary

Eight textile printing factories in Valencia, Spain, with a total workforce of 257 using spraying techniques were investigated as a result of severe interstitial lung disease occurring in three employees, one of whom died.

Clinical and radiological data together with biopsy specimens from 71 (27·6%) workers with abnormal respiratory features indicated the occurrence of an outbreak of organising pneumonia resulting in 6 deaths. Epidemiological analysis included the 22 workers who fulfilled the radiological case definition based on chest radiograph and computed tomographic scan showing widespread nodular opacities or confluent patchy consolidation with a lung biopsy corresponding to organising pneumonia. The overall attack rate was 8·9%. Only 2 of the 22 cases never worked in factories A or B. Those who had only worked in factory A had the highest risk of being a case (RR = 24·3; 95% CI = 5·7–104·4). The relationship of case status to period of employment suggested an abrupt change in exposure conditions in the period when Acramin FWR was substituted by Acramin FWN.

Although the precise toxicological mechanism is unknown, it is proposed that the lung disease was caused by spraying procedures delivered a respirable aerosol of Acramin FWN to distal airways and pulmonary parenchyma.

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Introduction

In April, 1992, 2 young women who worked in a textile factory were treated for interstitial lung disease and severe restrictive pulmonary insufficiency at the Hospital of Alcoi in the Autonomous Community of Valencia, Spain. Their illnesses were notified to the local health authorities. Epidemiological research carried out by the Public Health Department of the Community of Valencia related these two cases to a death caused by acute respiratory failure in February, 1992, in another woman who had worked in the same factory. These observations prompted an investigation of all printing textile factories that used spraying techniques in the area of Alcoi. Eight were identified with a total workforce of 257. Dye spraying had been introduced by these factories since 1987.

In this report we describe organising pneumonia associated with dye spraying and report epidemiological investigations of the outbreak as a result of which 6 persons died.

Patients and methods

Illness definition

All 257 employees were interviewed in a primary health care centre. Respiratory symptoms, smoking habits, and duration and characteristics of employments were assessed with a standardised questionnaire. Physical examination, spirometry, chest radiograph (CXR), and a computed tomographic (CT) scan were done in the Hospital of Alcoi. Workers in whom respiratory disease was suspected were referred to a hospital in Alicante for further evaluation.

In 71 (27·6%) of the 257 employees, there were one or more of the following findings: respiratory symptoms not attributable to any other evident disease, abnormal CXR, abnormalities of lung function, or intra-alveolar fibrin knots or organising pneumonia in lung biopsy (figure 1). The most frequently reported symptoms were productive cough, shortness of breath, chest pain, weight loss, and nose bleeding. CXR appearances and CT scans were consistent with the diagnosis of organising pneumonia. Among 88 subjects for whom an evaluable transbronchial lung biopsy was available, 68 showed definite abnormalities interpreted as minor changes—

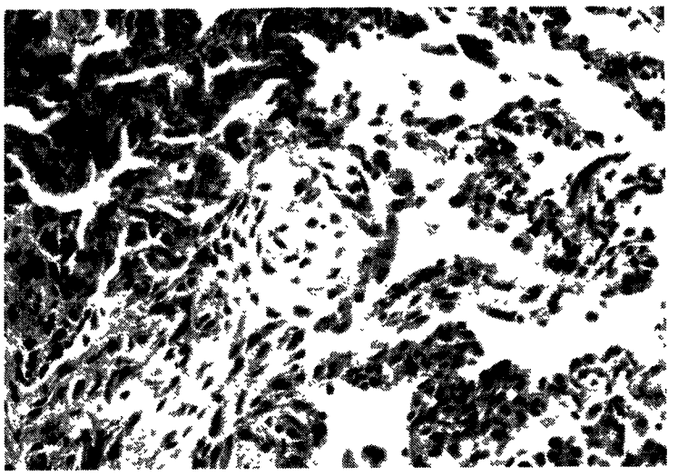


Figure 1: **Transbronchial biopsy showing intra-alveolar organisation and mild chronic inflammatory alveolar wall thickening**

Haematoxylin and eosin strain × 400.

increased numbers of macrophages—in 22 (20%); intra-alveolar knots of fibrin in 34 (39%); organising pneumonia in 13 (15%), 5 with associated interstitial fibrosis; and other changes in 1. 4 cases had open lung biopsies or examination of the lungs at necropsy, all showed characteristic features of organising pneumonia with associated interstitial fibrosis in some. Interstitial fibrosis in the absence of organising pneumonia was not detected.

All 71 workers with lung disease were treated with oral corticosteroids. After a minimum follow-up period of one year, 59 (83%) had recovered or were clinically stable; whereas deterioration, defined as a reduction in functional vital capacity of $\geq 15\%$ as compared with the initial assessment, occurred in 12. Of these 12 patients, 6 had died and 1 received a lung transplant. The remaining 5 are currently being treated with low doses of steroids and show stable or improving pulmonary function.

Epidemiological investigation

The eight factories (A to H) were inspected by an occupational hygienist from the Work Department of the Community of Valencia. The period studied was from when the factory begun to dye spray and April 31, 1992, when factory A was stopped dye spraying after one of the index cases died. All materials used in the factories from the date of onset of dye spraying were identified from factory registers, invoices, and interviews with employees. Aerosol sampling was undertaken in factories A and B. Total suspended particles were measured by using Guillain samplers, calibrated at 2 litres per min and operated for 2 hours.

All workers in each factory at any time during the study period, both current and past employments, were identified from factory files, public administration records, and interviews with workers.

A case definition which would minimise the possibility of false positives was selected for establishing the attack rates in the different factories. CXRs and CT scans of patients with organising pneumonia (figure 1) in whom lung biopsy was available, were reviewed. Two patterns were identified, widespread small nodular opacities (figure 2) or confluent patchy consolidation (figure 3). A case was defined when one of these patterns was found on the CXR, the CT scan, or both. CXRs and CT scans of all employees were assessed blindly by two independent radiologists. The agreement between radiologists was high (CXR film, κ 0·9; CT scan, κ 0·75; both chest radiograph and CT scan, κ coefficient 0·83). The radiologists considered that CXRs and CT scans fulfilled the case definition in 18 subjects and disagreed in 6. 4 of these 6 cases were considered to be cases by a third radiologist, resulting in 22 cases as a basis for further analysing the outbreak.

Attack rates were obtained by dividing the number of cases by the number of persons employed in each individual factory or in similar tasks within the factory. Since no relationship was found between the risk of disease and duration of exposure, outcomes were expressed as attack rates without the use of person-time denominators. Attack rates were stratified according to age, sex, and factory in which subjects were employed in order to obtain the corresponding rate ratios (RR). Confidence intervals were

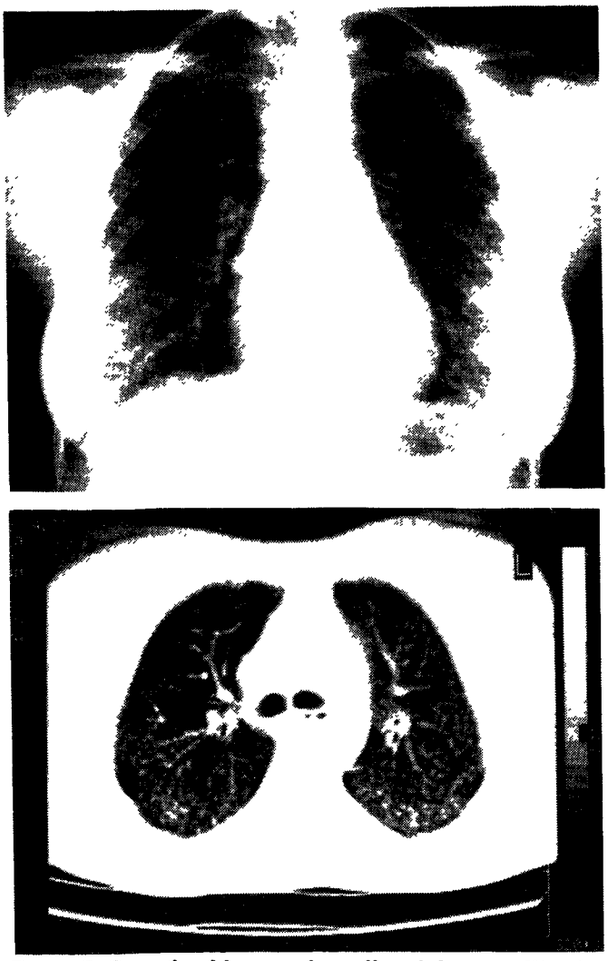


Figure 2: **Case 1: widespread small nodular opacities in CXR (top) and CT scan (bottom)**

obtained by the Miettinen method.[1] In order to assess the relationship between case status and period of time in which subjects had been employed, a case-control analysis was carried

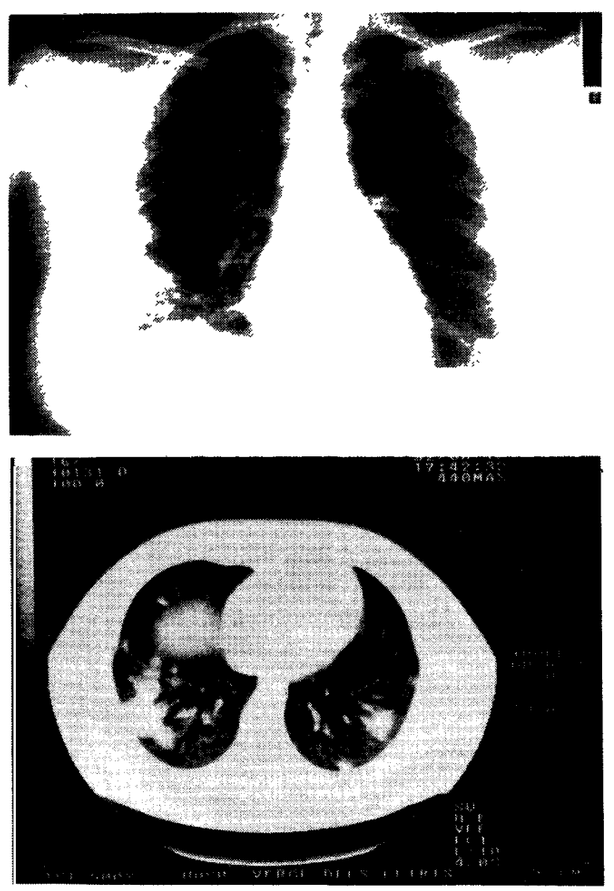


Figure 3: **Case 2: confluent patchy consolidation in CXR (top) and CT scan (bottom)**

Factory	Total	Men	Women
	No cases/no at risk	No cases/no at risk	No cases/no at risk
A	16/59 (27 1%)	1/14 (7 1%)	15/45 (33 3%)
B	4/29 (13 8%)	4/27 (14 8%)	0/2
C	1/7 (14 3%)	1/2 (50 0%)	0/5
D	1/42 (2 4%)	1/26 (3 8%)	0/16
E	4/104 (3 8%)	2/62 (3 2%)	2/42 (4 8%)
F	1/28 (3 6%)	0/7	1/21 (4 8%)
G,H	0/34	0/20	0/14
All subjects	22/257 (8 6%)	7/130 (5 4%)	15/127 (11 8%)
All factories	22/303	7/158	15/145

Table 1: **Distribution of 22 radiographically-affected subjects (cases) and the total 257 subjects at risk according to employment in different factories**

out. For each period of employment the measure of association was the cross-product ratio and the confidence intervals were calculated with the asymptotic method.[2]

Results

Table 1 shows the number of employees in each factory during the study period. The overall attack rate was 8·6%. The highest attack rate occurred in factory A (27·2%) followed by factory B (13·8%) and factory C (14·3%). Although the attack rate was twice as high in women (12·4%) as in men (5·7%) ($p < 0·01$), this was considered a reflection of the uneven sex distribution of the workforce and was not considered in the analysis.

Only 2 of the 22 cases had not worked in factories A or B or both. Since the high attack rate found in factory C was based on a single case, this factory was included in the reference category (not A or B). As shown in table 2 those who had only worked in factory A had a higher risk of being a case (RR = 24·3; 95% CI = 5·7–104·4), than those who had only worked in factory B (RR = 11; 95% CI = 1·9–62·9). The risk of being a case in those employed in factories A and B was higher among the sprayers and cleaners whose work involved direct contact with the aerosol products (attack rate 33·8%) than those employed in other tasks (10%) (RR of 3·38; 95% CI = 0·87–13·24).

4 cases who developed the disease after working for less than five months reported that symptoms had begun one month after entry to the factory. This pattern of acute disease with a short latency period prompted us to investigate whether the risk increased as a result of being exposed during a given period. An analysis of the relationship of case status to the period of time in which subjects had been employed showed that cases experienced a greater proportion of their employment during the periods between September and December, 1991, and January and April, 1992, as compared to the periods between September and December, 1990, and January and April, 1991 (table 3).

Since the attack rate in factory A was twice that in factory B, the concentrations of airborne aerosol in the two factories were compared. The concentration in factory A ranged from 5 to 16 mg/m^3 (mean 10 mg/m^3) as opposed to 1 to 3 mg/m^3 (mean 2 mg/m^3) in factory B.

30 different spray-printing related products were identified in the eight factories investigated. Factories A and B shared the use of five products throughout the study. In contrast, the other factories used a variety of agents, which were always different from those used in factories A and B.

It was noted that factories A and B experienced a change in formulation of two of the products used only by these factories. The first product was modified in January 1991, when one dye manufacturer reduced the concentration of diclor-2-propanol in the product Acrafix. The second product was modified in May 1991, when the same manufacturer changed the formulation of 'Acramin FWR' to 'Acramin FWN'. Acramin FWR, a powder, was modified to Acramin FWN, a liquid. The former was a product of the reaction of bis-diaminopropylmethylamine with hexamethylene di-isocyanate hexametilene, the latter (Acramin FWN) was obtained from diethylentriamine and adipic acid.

Factory	No cases/no at risk	Percent	Relative risk	95% CI
A	16/58	27 6	20 0	4 7–84 6
B	4/28	14 3	12 1	2 3–63 2
Not A or B	2/170	1 2	1	

Table 2: **Risk of being radiographically-affected according to employment in different factories**

Period	Cases	Controls	Odds ratio	95% CI
	(n=20) %/%	(n=57)* %/%		
Sep–Dec, 1990	65/35	65/35	1	0 54–1 86
Jan–April, 1991	65/35	58/42	1 34	0 73–2 48
May–Aug, 1991	60/40	51/49	1 44	0 79–2 63
Sep–Dec, 1991	80/20	42/58	5 52	2 81–10 91
Jan–April, 1992	85/15	54/46	4·83	2 34–10 06

Percentage of subjects employed/percentage of subjects unemployed. *Missing data on the time of exposure in 10 controls.

Table 3: **Proportion of radiographically-affected subjects (cases) and unaffected subjects (controls) for each period in factories A and B**

Discussion

The outbreak we investigated resulted in the death of 6 patients and the need for lung transplant in another. The lungs of all patients in whom specimens were available from open lung biopsy or necropsy examination showed histological features of organising pneumonia. Several cases also had evidence of interstitial fibrosis. It should be noted that all of these patients had been treated with high concentrations of inspired oxygen. However, pathological changes related to oxygen toxicity, particularly hyaline membrane formation, were not observed. Moreover, organising pneumonia is not a characteristic feature of oxygen toxicity. No evidence was obtained of relevant microbial infection in these patients.

Organising pneumonia of unknown origin was reported by Davison et al[3] who called it cryptogenic organising pneumonia and subsequently by Epler et al[4] who named it bronchiolitis obliterans with organising pneumonia, although changes described by these authors were primarily those of organising pneumonia. Isolated cases have been reported in association with connective-tissue diseases including rheumatoid arthritis; Sjögrens syndrome; scleroderma; ulcerative colitis; chronic active hepatitis; and consumption of drugs, in particular acebutolol, amiodarone, bleomycin, and cocaine.[5] More recently, seasonal organising pneumonia was reported in patients in the UK who developed recurrent episodes of organising pneumonia during the spring months of subsequent years, suggesting an unidentified environmental cause.[6]

Our investigations strongly suggest that pulmonary disease was caused by the inhalation of an aerosol from the Acramin-F process modified by the substitution of Acramin FWR with Acramin FWN. 20 of the 22 patients

including the 6 who died, had worked in factories A and/or B which were the only ones in which this product was used. Although textile dye spraying was undertaken in six other factories, Acramin FWR had been substituted by Acramin FWN only in factories A and B.

Acramin FWN was introduced in the Acramin F system by the manufacturer at the beginning of 1991, and had probably been used in both factories since June 1991. The index case in the outbreak was admitted to hospital in December 1991, and the 2 subsequent cases came to medical attention in April 1992. Our case-referent analysis of the risk of exposure to textile printing spraying among those fulfilling the case definition showed a statistically significant increase of risk of being employed during September to December 1991 and January to April 1992.

Factory A showed a twofold attack rate compared with factory B. Moreover, 5 of the 6 deaths occurred in employees of factory A; the other in factory B. This finding probably reflects the higher exposures to aerosol generated during dye spraying in factory A. Furthermore, the risk of disease was higher amongst those directly involved in spraying as compared to others employed in the same factory (31·6% *vs* 13·6%). Spray printing of textiles was stopped at factory A in May, 1992, and at factory B in July, 1992, since when no new cases have developed. Finally, no other cases of organising pneumonia were identified during the period of the outbreak in the local hospitals, among the general population, or among household contacts of the workers.

However, three subjects who fulfilled the case definition criteria had features discordant with our hypothesis. One man had worked in factory B but left employment in 1989, about two years before the introduction of Acramin FWN in the factory; radiological studies that qualified him for being a case were obtained three years after he had left the factory. The two other subjects had never worked either in factory A or B. Because our main purpose was to determine the cause of the outbreak of respiratory disease, we selected the case definition which was believed to be highly specific, in order to minimise the number of false positives which could hamper the strength of any causal relationships. Our radiological criteria, however, were not completely specific for the disease under study, so that false positives could have been included. The possibility that two of these three cases were false positives is supported by the findings of transbronchial lung biopsies, reported as normal in one case and showing only an increase in macrophages in the other; lung biopsy was not available for the third. Our case definition is also likely to have excluded a number of true cases (false negatives). We are aware of at least two, both of whom had evidence of organising pneumonia in their transbronchial lung biopsy, but who had normal findings on CXR. One of these had worked at factory A from September, 1990, to April, 1992, and the other at factory B from February, 1990, to 1992.

After our investigation was over, we found out that a similar outbreak of respiratory disease had occurred in Oran, Algeria. The Valencia Department of Public Health organised a field visit to the factory and a local hospital. The factory had learned the technique of textile spray printing in Alcoi and obtained the products from the same distributor who supplied factory B (factory A has obtained the dye directly from the manufacturer). Acramin FWR was received in October 1990; Acramin FWN in November, 1991, and first used in January, 1992. This factory employed 12 subjects to spray dyes onto fabrics. They worked on two adjacent tables. 6 of the 12 employees developed respiratory disease and 1 died. All 6 had abnormal CXRs, 4 with widespread nodular shadowing which would have fulfilled our case definition. The first case was attended by a physician in August, 1992, when she complained of respiratory symptoms since April, 1992, (some 3 to 4 months after the substitution of Acramin FWR for Acramin FWN). Both the clinical picture and the change of printing products a few months before the onset of symptoms are consistent with our hypothesis.

The Acramin system used for textile printing is marketed by the manufacturer as a three-component system (Acramin, Acramoll, Acrafix) to be mixed with water and applied with a brush or sponge. This technique is designed to polymerise rapidly as a lattice matrix on textiles without the need for heating or extensive drying time. Local factory modifications of the technique to improve adhesion to polyester fabrics include the substitution of a solvent (white spirits) for water as well as the application of the product as an aerosolised spray. Adverse health effects have not been recognised at worksites using the Acramin system without the addition of solvent or air-spraying techniques, with either the old formulation containing Acramin FWR or the new formulation containing Acramin FWN. Furthermore, factories A and B had used Acramin FWR without apparent health problems until its substitution by Acramin FWN. Toxicologic studies of the Acramin system components have been done only by ingestion and dermal application and not by inhalation.

Although there had been speculation that a polyfunctional aziridine used to improve printing performance could have been involved,[7] a check of all factories' invoices and interviews with employees did not provide evidence for this possibility. The fact that the same provider served factory B and the factory in Oran led us to consider the possibility of contamination during distribution. Factory A bought only on one occasion (January 1992) from the same provider as factories B and Oran, when the index case had already been admitted to hospital and when some of the cases had already showed clinical manifestations of the illness.

In consequence, we propose that the substitution of a solvent for water and the use of air spraying promoted the creation of a respirable aerosol of Acramin FWN. The mechanism of toxicity of Acramin FWN is unknown and its spray components are currently being evaluated. Further investigation of the toxicology of Acramin FWN and understanding its mechanism of lung injury may contribute to a better understanding of the cases of organising pneumonia.

The aetiology of this outbreak has been strongly linked to the use of the spraying technique for textile printing. As far as we know, this technique in Spain is mostly restricted to the area of Alcoi where traditionally there have been many small specialised factories. It should be noted that the owners of the Oran factory learnt about this technique in Alcoi. We do not know, however, how widespread the use of the spraying technique is in other countries. Other respiratory diseases caused by the inhalation of reformulations of old products such as leather sprays or waterproofing agents have been recently reported.[8,9] These product reformulations were attempts to eliminate ozone-depleting solvents and propellants from the aerosol sprays. The potential for serious adverse health effects of product modifications are underscored by these reports and the results of our investigation.

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Evaluation of efficacy of liver transplantation in alcoholic cirrhosis by a case-control study and simulated controls

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Summary

To assess the efficacy of liver transplantation in patients with alcoholic cirrhosis, we compared 2-year survival of 169 liver transplantation patients in 12 French centres with survival of two control groups treated conservatively.

The matched group was 169 patients of similar age, cirrhosis severity, and bleeding history; the simulated group was 169 patients whose theoretical survival was determined in a cohort of 797 patients with alcoholic cirrhosis. The probability of survival to 2 years in transplanted patients was 73 (95% confidence interval 67–79%) versus 67% (59–75) in the matched and 67% (63–71) in simulated controls. When prognostic factors were taken into account, transplantation was associated with survival ($r = 0{\cdot}527$; $p = 0{\cdot}069$). Patients with severe liver disease (high-risk group) benefited most for 2-year survival: 64% (42–86) *vs* 41% (23–59) in the matched and 23% (19–27) in the simulated control groups ($p < 0{\cdot}01$). There was no difference for patients at low and at medium risk.

Liver transplantation increases the 2-year survival of patients with severe alcoholic cirrhosis. In patients with less severe disease, further studies should be done by non-randomised controlled studies with longer follow-up or by randomised trials.

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Introduction

Liver transplantation is a lifesaving treatment in various end-stage liver diseases, including alcoholic cirrhosis.[1-4] However, no randomised trials have been done to evaluate the procedure, and because there has been marked improvement since 1981 in survival after transplantation, randomisation of patients with advanced liver disease to a non-transplantation control group is inappropriate. Markus et al[5] evaluated the efficacy of transplantation for patients with primary biliary cirrhosis by simulated controls in whom survival was estimated from a prognostic model, the Mayo model.[6]

Following the same strategy, we used a cohort of patients with alcoholic cirrhosis from the Antoine Béclère Hospital in Clamart, France and designed successive proportional-hazards prognostic models.[7-10] A final model, the Beclere model, was validated with internal controls and an independent population of patients with alcoholic cirrhosis then applied to a population of patients with alcoholic cirrhosis who underwent transplantation in 12 French centers. Actual survival after transplantation was compared with simulated survival using the Beclere model.

To improve the comparison, we also did a case-control study; each transplanted patient was matched to a control patient for age, severity of cirrhosis, and bleeding history. Survival after transplantation was compared with the survival of simulated and matched controls.

Methods

Simulated controls: Beclere model

The Beclere model is a proportional-hazards prognostic model that uses a small number of inexpensive, non-invasive, widely available