

ORIGINAL ARTICLE

Systemic sclerosis and occupational risk factors: a case-control study

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Systemic sclerosis (SS) has been defined as a generalised disorder of the small arteries, microvessels, and the diffuse connective tissue, characterised by scarring (fibrosis) and vascular obliteration in the skin, gastrointestinal tract, lungs, heart, and kidneys.¹ The aetiology of SS is unknown, but it is probably caused by both endogenous and exogenous factors. Among the exogenous factors, several types of occupational exposure have been suggested as potential causes of SS. Association between SS and silica exposure was reported first. A study among South African gold miners in 1957 suggested that silica was an aetiological factor in SS.² Later, larger epidemiological studies such as the case-control study of Sluis-Cremer *et al* confirmed the link between silica exposure and SS.³ Exposure to certain organic compounds such as vinyl chloride monomers, trichlorethylene, benzene, and other solvents was also reported as a risk factor of SS in case reports and in two case-control studies.^{4,5}

To investigate further the relation between systemic sclerosis and occupational exposure, a case-control study involving 80 systemic sclerosis patients and 160 controls was carried out between 1998 and 2000.

METHODS

Patients

Eighty incident or prevalent case patients with SS admitted consecutively to the Department of Internal Medicine at the University Hospital of Tours from 1998 to 2000 were included in the study. SS was defined according to the American Rheumatism Association criteria¹; patients with localised variants of scleroderma (for example, morphea or linear scleroderma) were therefore excluded. Two stages of cutaneous extension according to the classification of Leroy and colleagues⁶ were represented in the study population: 54 patients had limited scleroderma, and 26 patients had diffuse scleroderma.

Aims: A case-control study was carried out between 1998 and 2000 to investigate the relation between systemic sclerosis and occupational exposure.

Methods: Eighty cases of systemic sclerosis admitted consecutively to the Department of Internal Medicine at the University Hospital of Tours from 1998 to 2000 were included. For each case, two age, gender, and smoking habits matched controls hospitalised during the same period in the same department were selected. A committee of experts was set up retrospectively to assess occupational exposure. Exposure to silica dust and organic solvents (such as trichlorethylene and other chlorinated solvents, and benzene and other aromatic solvents) was investigated using semiquantitative estimates of exposure. An exposure score was calculated for each subject based on probability, intensity, daily frequency, and duration of exposure for each period of employment. The final cumulative exposure score was obtained, taking into account all periods of employment.

Results: Significant associations with SS were observed for crystalline silica, trichlorethylene, chlorinated solvents, toluene, aromatic solvents, ketones, white spirit, epoxy resins, and welding fumes. Risk of SS was significantly associated with a high final cumulative exposure score of occupational exposure to crystalline silica, trichlorethylene, chlorinated solvents, welding fumes, and any types of solvents.

Conclusion: Results confirm the influence of occupational risk factors in the occurrence of SS in both men and women. The link is not only with silica but also with other compounds such as solvents.

Two age (± 3 years), gender, and smoking habits matched controls were selected for each case from the same computerised admission file in our department. The patients were matched on their smoking habits (that is, frequency and quantity) because tobacco use could not be ruled out as a potential confounding factor. Controls were hospitalised during the same period in the same department as the cases. The controls all suffered from chronic illnesses, most of which (for example, diabetes, arterial hypertension, and cardiovascular disease) required repeated hospitalisation. Subjects with connective tissue disease, known autoimmune systemic disease, neoplasia, or chronic interstitial lung disease were excluded from the study.

All patients and controls came from the same geographical region—that is, the six departments of the central region of France.

Data collection

All subjects agreed to a 30 minute interview by a trained investigator who was not aware of the case-control status. A structured questionnaire containing the following items was used: socioeconomic and personal characteristics, and complete medical and occupational histories. Exposure to silica dust, silicon, vinyl chloride, welding fumes, organic solvents (chlorinated, aromatic, etc), white spirit, formaldehyde, epoxy resins, pesticides, and hand-arm vibration were especially investigated. Drinking habits, use of medication, lifestyle (for example, gardening, do-it-yourself) were investigated. Information was collected on smoking habits of cases and controls. Subjects were classified into groups of smokers and non-smokers. Former smokers were classified as smokers if the cessation of tobacco consumption was within five years; otherwise, they were classified as non-smokers. Tobacco consumption was quantified in pack years. Patients were also

Table 1 Main descriptive data of 80 cases of systemic sclerosis and 160 matched controls

Exposure	Cases	%	Controls	%
Sex				
Male	11	13.8	22	13.8
Female	69	86.2	138	86.2
Age (years)				
Mean (SD)	55.8 (15.3)		56.4(15.6)	
Smoking habits				
Non-smokers	63	78.7	126	78.7
Smokers	17	21.3	34	21.3
Age at disease onset (years)				
Mean (SD)	47.8 (15.1)		-	-
Cutaneous extension				
Limited scleroderma	54	67.5	-	-
Diffuse scleroderma	26	32.5	-	-

Table 2 Risk associated with occupational exposure among 80 cases of systemic sclerosis and 160 matched controls; maximum likelihood estimate of the odds ratio (OR) and confidence intervals (95% CI)

Exposure†	Cases n=80	Controls n=160	OR (95% CI)
Crystalline silica	10	4	5.57 (1.69 to 18.37)**
Trichlorethylene	13	12	2.39 (1.04 to 5.22)*
Chlorinated solvents	16	14	2.61 (1.20 to 5.66)*
Toluene	8	5	3.44 (1.09 to 10.90)*
Aromatic solvents	11	9	2.67 (1.06 to 6.75)*
Ketones	8	2	8.78 (1.82 to 42.38)**
White spirit	15	10	3.46 (1.48 to 8.11)**
Any type of solvent	22	20	2.66 (1.35 to 5.23)*
Epoxy resin	6	3	4.24 (1.03 to 17.44)*
Welding fumes	7	4	3.74 (1.06 to 13.18)*

†Ever versus never exposed; *p<0.05; **p<0.01.

questioned about other potential confounding factors such as silicone implants, cosmetic surgery, and the dyeing of hair.

Assessment of exposure

A committee of six experts, comprised of three occupational physicians, two epidemiologists, and one industrial hygienist, was set up retrospectively to assess occupational exposure. Exposure assessments were semiquantified for cases and controls based on the experts' knowledge of the industrial process and its evolution over time.

All employment periods in which a subject had worked for more than six months were recorded. For each patient and their respective controls, only employment corresponding to the time period prior to the patient's diagnosis was included.

Exposure to silica dust and organic solvents (such as trichlorethylene and other chlorinated solvents, and benzene and other aromatic solvents) was investigated using semi-quantitative estimates of exposure. An exposure score was calculated for each person's employment period during which exposure to each of these toxic agents occurred. This exposure score took into account the probability of exposure (probability score of 0 = non-exposure, 0.25 = possible exposure, 0.75 = probable exposure, and 1 = certain exposure); intensity of exposure (intensity score from 0 for non-exposure to 4 for highest level of exposure); frequency of exposure (with a frequency score based on length of time worked daily: <10% = 0.05, 10–50% = 0.30, and >50% = 0.75); and duration of exposure (number of years worked). Finally, the exposure score for each employment period was expressed as probability × intensity × frequency × duration.

The final cumulative exposure score for a given subject was expressed as the sum of employment exposure scores, taking into account all periods of employment. Subjects with a final

cumulative exposure score >1 were considered as having a high score for occupational exposure. For example, a subject was exposed to crystalline silica during an initial period of five years with a certain exposure (1), a middle intensity (2), and a frequency of 10–50% (0.30). For this period, the exposure score is: $5 \times 1 \times 2 \times 0.30 = 3$. He was exposed during a second period of two years, with a probable exposure (0.75), a middle intensity (2), and a frequency of less than 10% (0.05). For this second period, the exposure score is: $2 \times 0.75 \times 2 \times 0.05 = 0.15$. The final cumulative exposure score is: $3 + 0.15 = 3.15$.

Statistical analysis

To evaluate the association between SS and risk factors, a conditional maximum likelihood estimate of the odds ratio (OR) and 95% confidence intervals (95% CI) were calculated using Epi-Info 6.04cFr software.

For analysis of exposure scores, comparisons were made between subjects with high final cumulative scores for their employment lifetime and those without a high final cumulative score.

A p value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 presents the socioeconomic data of cases and controls (sex, age, and smoking habits). Continuous demographic variables were expressed as mean (SD). No differences were observed between cases and controls for sex ratio, age, and smoking habits. Furthermore, the socioeconomic levels and professional categories were similar.

Other potential confounding factors were analysed in men and women. History of silicone implants, cosmetic surgery, or frequent dyeing of hair was not reported by any of the patients

Table 3 Risk associated with high final cumulative exposure score in 80 cases of systemic sclerosis and 160 matched controls; maximum likelihood estimate using odds ratio (OR) and confidence intervals (95% CI)

Exposure	Cases n=80	Controls n=160	OR (95% CI)
Crystalline silica	7	4	3.74 (1.06 to 13.18)*
Trichlorethylene	7	2	7.58 (1.54 to 37.36)**
Chlorinated solvents	8	4	4.33 (1.26 to 14.86)*
Toluene	3	1	6.19 (0.63 to 60.53)
Aromatic solvents	6	4	3.16 (0.87 to 11.55)
Ketones	5	0	Non-calculable
White spirit	6	4	3.16 (0.87 to 11.55)
Any type of solvents	17	12	3.32 (1.50 to 7.37)**
Epoxy resin	3	1	6.19 (0.63 to 60.53)
Welding fumes	6	2	6.41 (1.26 to 32.49)*

*p<0.05; **p<0.01.

Table 4 Risk associated with occupational exposure among female cases of systemic sclerosis and matched controls; maximum likelihood estimate of the odds ratio (OR) and confidence intervals (95% CI)

Exposure†	Cases n=69	Controls n=138	OR (95% CI)
Crystalline silica	6	1	13.04 (1.54 to 110.66)*
Trichlorethylene	6	6	2.10 (0.65 to 6.75)
Chlorinated solvents	9	8	2.44 (0.90 to 6.63)
Toluene	5	3	3.51 (0.81 to 15.17)
Aromatic solvents	7	6	2.48 (0.80 to 7.70)
Ketones	7	2	7.68 (1.55 to 38.02)*
White spirit	8	3	5.90 (1.51 to 23.01)*
Any type of solvent	14	14	2.25 (1.01 to 5.05)*
Epoxy resin	3	0	Non-calculable
Welding fumes	2	1	4.09 (0.36 to 45.90)

†Ever versus never exposed; *p<0.05.

Table 5 Risk associated with occupational exposure among male cases of systemic sclerosis and matched controls; maximum likelihood estimate of the odds ratio (OR) and confidence intervals (95% CI)

Exposure†	Cases n=11	Controls n=22	OR (95% CI)
Crystalline silica	4	3	3.62 (0.64 to 20.40)
Trichlorethylene	7	6	4.67 (0.99 to 21.89)
Chlorinated solvents	7	6	4.67 (0.99 to 21.89)
Toluene	3	2	3.75 (0.52 to 26.84)
Aromatic solvents	4	3	3.62 (0.64 to 20.41)
Ketones	1	0	Non-calculable
White spirit	7	7	3.75 (0.82 to 17.17)
Any type of solvent	8	6	7.11 (1.40 to 36.12)*
Epoxy resin	3	3	2.37 (0.39 to 14.38)
Welding fumes	5	3	5.28 (0.96 to 28.9)

†Ever versus never exposed; *p<0.05.

included in the study. Use of drugs already implicated in the development of SS (for example, anorexigens, bleomycin, carbidopa) was also not reported. Tobacco consumption was not significantly different between cases and control smokers (median = 15 pack tobacco years in each group).

Table 2 indicates risks associated with occupational exposure in the 80 cases and the 160 matched controls. Significantly increased ORs for SS were observed for crystalline silica (OR 5.57, 95% CI 1.69 to 18.37), trichlorethylene (OR 2.39, 95% CI 1.04 to 5.22), chlorinated solvents (OR 2.61, 95% CI 1.20 to 5.66), toluene (OR 3.44, 95% CI 1.09 to 10.90), aromatic solvents (OR 2.67, 95% CI 1.06 to 6.75), ketones (OR 8.78, 95% CI 1.82 to 42.38), white spirit (OR 3.46, 95% CI 1.48 to 8.11), epoxy resins (OR 4.24, 95% CI 1.03 to 17.44), and welding fumes (OR 3.74, 95% CI 1.06 to 13.18).

The study population consisted of 69 females and 11 males. Among the women, significantly increased ORs for SS were

observed for crystalline silica, ketones, white spirit, epoxy resins, and any organic solvents (table 4). No correlation was found among men between occupational exposure and SS except for solvents as a whole (table 5).

Table 3 indicates risks associated with high final cumulative exposure score in the 80 cases and 160 matched controls. Significantly increased ORs for SS were observed for crystalline silica (OR 3.74, 95% CI 1.06 to 13.18), trichlorethylene (OR 7.58, 95% CI 1.54 to 37.36), chlorinated solvents (OR 4.33, 95% CI 1.26 to 14.86), welding fumes (OR 6.41, 95% CI 1.26 to 32.49), and any type of solvents (OR 3.32, 95% CI 1.50 to 7.37).

No association between hand–arm vibration and SS was found, especially for patients exposed to silica or solvents, epoxy resin, or welding fumes (data not shown).

According to the clinical data, 54 patients (67.5%) had limited scleroderma and 26 (32.5%) had diffuse scleroderma. No

difference was observed in terms of occupational exposure between the two degrees of cutaneous extension.

DISCUSSION

This case-control study confirms that occupational exposure to crystalline silica and certain organic solvents (aromatic, chlorinated) is associated with an increased risk of SS. It also shows significant associations between SS and other occupational chemical compounds: ketones, epoxy resins, white spirit, and welding fumes.

Our study population was homogeneous because only SS patients were included, in contrast with other case report studies in which systemic and localised variants of scleroderma were included.⁴ Patients with cancer, autoimmune disease, and chronic interstitial lung disease were excluded to avoid overmatching of controls, thereby minimising the risk associated with occupational exposure to chemical agents. Consequently, odds ratios could have been overestimated. However, the controls were selected from patients with diagnoses, some of which might have an occupational origin, such as respiratory disease. Moreover, odds ratios for silica and solvent exposure were close to those found in previous studies.

The hypothesis that occupational exposure could increase the risk of autoimmune disorders has been reported in the literature for SS patients in case reports and a few case-control studies.³⁻⁵

The role of silica exposure has been described in detail. In 1957, Erasmus² reported the high prevalence of SS in gold miners exposed to dust containing a high percentage of free silica. These findings were confirmed by Rodman and colleagues,¹² who reported prolonged and heavy exposure to silica dust in 60 SS men. Sluis-Cremer and colleagues³ conducted a case-control study in which "cumulative lifetime silica exposure" was shown to be significantly higher in cases compared with controls.

The prevalence of SS in our study was strongly associated with both occupational exposure to silica (OR 5.57, $p < 0.01$) and cumulative lifetime exposure (OR 3.74, $p < 0.05$). The role of welding fumes could not be dissociated from that of silica because such exposure occurred simultaneously in six subjects.

Exposure to chemical compounds, including organic solvents, has also been reported to be involved in the development of SS. Reinl¹³ reported a case of a young woman who degreased aluminium parts with trichloroethylene for three years and developed diffuse SS. Since this first report, many case reports have suggested a link between occupational exposure to solvents and SS. Only seven case-control studies have been conducted to confirm this hypothesis.^{4, 5, 7-11} The two major studies were those of Nietert and colleagues⁵ and Bovenzi and colleagues.⁴ In the Nietert *et al* study, 178 patients with SS were compared to 200 controls. Men with SS were more likely than controls to have high cumulative intensity scores (OR 2.9) and high maximum intensity scores (OR 2.9) for solvent exposure, as well as high maximum intensity scores for trichloroethylene exposure (OR 3.3). In the Bovenzi *et al* study, 21 patients with SS were compared with 42 controls. A significant association was found between exposure to organic solvents and scleroderma (OR 9.28), although this occurred only among men. Czirjak and colleagues⁷ found only a greater proportion of SS in patients exposed to chemicals, while Goldman⁸ found a greater proportion in those exposed to organic chemicals. In Silman and Jones' prospective study¹¹ and Lundberg and colleagues' retrospective study,¹⁴ a significant proportion of patients with SS were exposed to organic solvents, but the relation was not significant. Finally, in a brief report, Laing and colleagues⁹ noted a significant risk of SS in patients exposed to trichloroethane (OR 5.86) and trichloroethylene (OR 2.19), and

Schaefferbeke and colleagues¹⁰ reported a high risk in patients exposed to solvents, epoxy resins, silicates, cement, and pesticides (OR 2.69).

Our results confirm that the risk of SS is associated with occupational exposure to some organic solvents, especially trichloroethylene and chlorinated solvents for which the risk is significantly related to high final cumulative exposure score.

Among SS patients, occupational exposures were varied. Most cases exposed to crystalline silica were workers in pottery or porcelain factories, foundry workers, and welders. Exposure to trichloroethylene mainly resulted from the cleaning of metal in various occupations. The building trade was the predominant activity of those who had been exposed to white spirit and epoxy resin. Exposure to aromatic solvents was present mainly among individuals in chemistry related occupations and in workers exposed to petrol. All SS patients exposed to welding fumes were workers involved in welding activity. There was no predominant occupation among cases exposed to ketones.

The main duration of exposure was more than 10 years in SS patients exposed to silica, chlorinated solvents, white spirit, epoxy resin, ketone, or welding fumes. Mean duration of exposure of less than 10 years was only found for aromatic solvents (8.9 years). Certain lengths of exposure were shorter, approximately 4-5 years, but with higher level daily exposures. The cases with the highest exposure scores were, for the most part, those with periods of exposure that exceeded 15 years, with probability of exposure rated as "certain" and daily frequency of exposure of at least 50%. On the other hand, the time between the last exposure and diagnosis (latency period) for these patients averaged 47 months for the solvents and 41 months for the silica. With respect to these two exposures, more than half of the subjects had a latency period equal to 0.

As some subjects had several periods of exposure to occupational risk factors, the categories of exposure were not mutually exclusive, especially for solvent exposures that often occur simultaneously (for example, ketones and chlorinated solvents simultaneously present in five patients, chlorinated solvents and white spirit in eight patients). Our study was not large enough to take this problem into account by multivariate analysis. We therefore calculated risk estimates separately for the main solvents and solvent categories and found a clear increased risk of SS for several of these toxic agents. These results are similar to those of Nietert and colleagues,⁵ especially for trichloroethylene and chlorinated solvents, for which the strength of the relation between exposure to solvents and the risk of SS was confirmed by high scores of cumulative exposure.

To our knowledge, the link between SS and solvents such as toluene, aromatic solvents, ketones, and white spirit has never been reported in a case-control study. Further studies are necessary to identify the specific impact of each of these compounds, as some of them coexist in the workplace. It is of interest that no potential confounding factor (silicone implants, cosmetic surgery, or use of drugs involved in the development of SS) was identified in our patients.

Moreover, we found an increased and significant risk of SS among women for crystalline silica, ketones, white spirit, and epoxy resins as well as for organic solvents in general, in contrast to the findings of Nietert and colleagues,⁵ which did not show a relation between solvent exposure and risk of SS in women. These authors indicated that their job exposure matrix was not sensitive enough to detect the variations in exposure in women, or might not reflect differences in exposure of men and women with the same job titles. In addition, their study did not address exposure to household cleaning agents or other environmental factors. Exposure to household cleaning agents such as bleach was considered in our study, and we found no relation with SS.

Hand-arm vibration exposure was exceptional in our main female population, even in workers exposed to silica. These

data can explain the lack of association between SS and hand–arm vibration exposure in this study.

There were only 11 cases of male SS patients. Consequently, the association between SS and occupational risk factors was only found for solvents as a whole; the results were not statistically significant for recognised risk factors such as silica.

Information bias or differential misclassification in occupational exposure should not have occurred because interviewers, experts, and personnel involved in exposure data coding were blind to the case–control status of the subjects.

The mechanisms of a relation between occupational factors and autoimmune diseases including SS are not clear.¹⁵ For crystalline silica, Vigliani and Pernis¹⁶ suggested as early as 1963 that autoimmune phenomena were involved in the pathogenesis of SS. Subsequent experimental studies of the immunological effects of silica administered intratracheally and intravenously showed that silica was responsible for changes in cellular and humoral immune responses associated with depression of T cell function.¹⁷ Hausteine and colleagues⁸ suggested that small inhaled particles of quartz (<10 µm) coming into contact with the lungs were probably responsible for immunological changes, such as stimulation of production of macrophages and interleukin 1, platelet derived growth factor, and fibronectin. Finally, production and destruction of macrophages to attack silica particles are responsible for stimulation of collagen synthesis. Macrophage production and destruction cycles and the presence of particles in the lymph stimulate T helper and B cell responses and immune disorders. Goldman⁸ suggested that chemical solvents may stimulate SS by penetration through the skin and denaturation of proteins and then stimulation of autoimmune responses. Bovenzi and colleagues⁴ hypothesised that solvents have double penetration: through the skin and by inhalation (made possible by their high volatility). After penetration, solvents bind to nucleic acids and proteins, reduce humoral and cell mediated immune responses,^{5,19} and stimulate the production of fibrogenic proteins and growth factors such as interleukin 1, platelet derived growth factor, transforming growth factor β, and fibronectin, which are generated in scleroderma.²⁰ In addition, exposure to trichlorethylene and a metabolite of trichlorethylene has been shown to induce development of autoimmune responses (antinuclear, DNA, and anticardiolipin antibodies^{5,21}).

In conclusion, our case–control study confirms the influence of occupational risk factors in the occurrence of SS. The link is not only with silica, but also with other compounds such as trichlorethylene, chlorinated solvents, and solvents in general. This association occurs in the whole SS population, regardless of sex.

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