Systemic Sclerosis and Occupational Risk Factors: Role of Solvents and Cleaning Products

ANNE MAÎTRE, MARTINE HOURS, VINCENT BONNETERRE, JOËLLE ARNAUD, MARIE TÜLIN ARSLAN, PATRICK CARPENTIER, ALAIN BERGERET, and RÉGIS DE GAUDEMARIS

ABSTRACT. ***Objective.*** To analyze occupational and non-occupational exposure factors suspected of being associated with scleroderma (SSc), with a view to inculpating or excluding certain potentially toxic substances (e.g., solvents), thereby contributing to the recognition of such toxins in the field of occupational health.

Methods. The study comprised 10 men and 83 women diagnosed with SSc between 1995 and 1999 (American College of Rheumatology criteria) and early SSc, and 206 age and sex matched controls. The SSc registry is all-inclusive in the French administrative departments of Isère and Savoie so controls were randomly selected from the general population (using telephone directories) in these departments to ensure full representation. Exposure factors were analyzed for each subject by a personal questionnaire, and an individual evaluation was carried out by an industrial expert. Data were analyzed by conditional logistical regression adjusting for educational level.

Results. Construction workers were at significantly higher risk of contracting SSc; odds ratio (OR) = 4.01 (95% confidence interval 1.14-14.09). Analysis by industrial experts identified exposure to certain toxic substances regularly used by these same workers as risk factors for SSc: cleaning products: OR = 1.66 (0.90-3.08) (both sexes) and OR = 1.71 (0.92-3.20) (women only); solvents: OR = 3.23 (1.58-6.63) (both sexes) and OR = 2.80 (1.28-6.11) (women only); synthetic adhesives: OR 25.36 (1.36-472.28) (on 3 exposed cases).

Conclusion. Exposure to either cleaning products or solvents emerged as a risk factor for SSc. Exposure factors should be characterized and results of all studies compared to implement appropriate preventive measures in relevant workplaces. (J Rheumatol 2004;31:2395–401)

Key Indexing Terms:
SCLERODERMA — SYSTEMIC SCLEROSIS — OCCUPATIONAL EXPOSURE
SOLVENTS — CLEANING PRODUCTS

Systemic scleroderma (SSc) is a rare chronic disease with a very serious prognosis (35% mortality rate within 5 years). The disease usually first appears between 40 and 50 years of age[1]. The etiology is unknown and the epidemiology is poorly characterized. Its prevalence varies between 0.1 and 13.8 per 100,000 inhabitants, depending on the study[1-6], with a sex ratio for women between 1.8 and 15.

SSc is recognized in France as an occupational disease resulting from exposure to crystalline silica[6a]. A number of studies have mentioned the possible role of occupational exposure to solvents, but not all the results have been conclusive[7-9]. Exposure to other chemical substances has also been suspected, including epoxy resins[10], formaldehyde[1], and pesticides[10,11]. Possible environmental risk factors include hair dyes[12], silicon breast implants[13,14], and pets[10], although a role has not been confirmed for any of these by epidemiological data.

Our aim was to identify forms of occupational exposure that could account for the occurrence of SSc in the French administrative departments of Isère and Savoie. These departments maintain a quasi-exhaustive registry for this disease by means of a system in which new cases are noted by medical specialists in the organs affected by the disease, i.e., dermatologists, rheumatologists, vascular specialists, and internal medicine specialists. This registry revealed that the incidence of SSc is higher in certain heavily industrial-

From the Environnement et Prédiction de la Santé Des Populations — Laboratoire, Faculté de Médecine, Domaine de la Merci, La Tronche; Unité Mixte de Recherche Epidémiologique Transport Travail Environnement, Université Claude Bernard, Lyon; Laboratoire de Médecine Vasculaire, CHU Grenoble, Grenoble, France.

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A. Maître, PhD, Environnement et Prédiction de la Santé Des Populations — Laboratoire, Faculté de Médecine, Domaine de la Merci; M. Hours, PhD, Unité Mixte de Recherche Epidémiologique Transport Travail Environnement, Université Claude Bernard; V. Bonneterre, MD; J. Arnaud, MD, Environnement et Prédiction de la Santé Des Populations — Laboratoire, Faculté de Médecine, Domaine de la Merci; M.T. Arslan, Unité Mixte de Recherche Epidémiologique Transport Travail Environnement, Université Claude Bernard; P. Carpentier, MD, Laboratoire de Médecine Vasculaire, CHU Grenoble; A. Bergeret, MD, Unité Mixte de Recherche Epidémiologique Transport Travail Environnement, Université Claude Bernard; R. de Gaudemaris, MD, Environnement et Prédiction de la Santé Des Populations — Laboratoire, Faculté de Médecine, Domaine de la Merci.

Address reprint requests to Professor R. de Gaudemaris, Equipe Médecine et Santé au Travail EPSP, Laboratoire TIMC UMR 5525, Faculté de Médecine, Domaine de la Merci 38706 La Tronche Cedex, France. E-mail: RDegaudemaris@chu-grenoble.fr

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ized areas within the departments, especially those associated with the chemical and metal industries[15], in comparison with non-industrial areas.

MATERIALS AND METHODS

An epidemiological case-control study was carried out, including all cases of SSc diagnosed and notified to the registry between January 1, 1995 and December 31, 1999. The survey, started at the beginning of 1997, required contacting cases who had been diagnosed up to 2 years prior to this date. Other cases were contacted immediately after diagnosis.

Definition of cases. All patients live in the 2 geographical areas covered by the registry (the administrative departments of Isère and Savoie) investigated in the hospital and meet most criteria of the 1980 American College of Rheumatologists (ACR) classification[16] (proximal or metacarpophalangeal sclerosis), or 2 of the 3 minor criteria (sclerodactyly, digital pitting scars, or bibasilar pulmonary fibrosis). Also included are cases with signs of early SSc, namely a combination of Raynaud's phenomenon (RP), confirmed by a color game test[17], and either a capillary microscopy pattern typical of SSc or any of the antinuclear antibodies considered specific (anti-centromere, anti-Scl 70, or nucleolar) measured by fluorescence. Patients fulfilling criteria of any other connective tissue disease were excluded (no overlap syndrome), and capillary abnormalities were taken into account only if they showed a clear SSc pattern according to Maricq[17], either the active or the slow patterns. Classification of each case was systematically reviewed by 2 clinicians, one of whom specializes in SSc. Among eligible cases, 2 patients (2,1%) were not included as they died and had no family available for the interview.

Selection of controls. Since all cases of SSc were listed in the administrative regions studied, controls could be randomly selected from the general population in these 2 regions. Two controls were selected for each female case, and 4 for each male case. Matching was done on the basis of age (using 5-year periods). Controls were contacted by telephone from a randomly compiled list of numbers in the 2 regions. In these regions more than 95% of families have telephone number. Only those numbers corresponding to the main residence of a private citizen were used. Each number was called up to 5 times at different times: in the morning, at lunchtime, in the afternoon, and in the evening during the week, and once during the weekend. If there was no response to any of these calls, the next number on the list was used.

The person answering the phone was asked about the people in the house 18 years of age and over to select a control of the appropriate age. The interview confirmed that the subjects were eligible if they had no SSc, cancer, severe respiratory disease, or RP to avoid overmatching; no controls were eliminated for such reasons. The questionnaire for RP included 5 questions, validated in a preliminary survey: (1) Are your fingers sensitive to cold? (2) Do any of your fingers sometimes become unusually white? (3) Do any of your fingers sometimes become unusually blue? (4) Have you ever had spontaneous skin ulcerations in the fingers? (5) Have you ever been diagnosed with RP? Only people who answered no in each case were selected as controls. Any yes, in the past, or don't know response was considered a criterion for exclusion. Among controls selected through this process, 4% declined to participate in the screening survey. All who participated in the screening survey were eligible, based on medical criteria and all controls completed the full telephone interview regarding occupational history.

Evaluation of occupational exposure. Questionnaires were mailed to both cases and controls to prepare for the phone interview that occurred few days later. For cases, only employment prior to diagnosis of SSc was investigated. The questions included occupational details (place of employment and functions without minimum duration); suspected forms of occupational exposure, either in terms of contact with potential toxins (paints, varnishes, adhesives, epoxy resins, hydrocarbons, monomeric vinyl chloride, inks, hair and fabric dyes, cutting oils, pesticides, siliceous sand or ore, disinfectants, and materials used in the manufacture of plastics) or certain specific working conditions (dust-laden atmospheres, vibrating machines, and contact with animals) together with details on lifestyle and non-occupational risk factors (type of residence, smoking, history of miscarriage, silicon breast implants, use of appetite suppressants, use of hair dyes, and presence of pets). During the telephone interview, which lasted about one hour (for each case and control) and was conducted by an occupational health specialist unaware whether the interviewee was a case or a control subject, all responses to this questionnaire were checked and collected. Further occupational details were accumulated with specific questions for those doing certain kinds of work.

Every job was classified by a group of experts (including occupational health specialists and industrial safety experts) according to the potential level of exposure to toxins on a 3-level scale: zero or low, moderate, and high. The criteria used for this classification were likelihood of exposure, duration of exposure, intensity of exposure, and percentage of working time exposed. The following specific forms of exposure were documented: silica, abrasive products (such as corundum or silicon carbide, or abrasive powder), monomeric vinyl chloride, formaldehyde, epoxy resins, organic solvents in general, and more specifically aliphatic solvents, halogenated solvents, BTX-solvents (solvents containing more than 5% benzene, toluene, or xylene), pesticides, dyes, disinfectants, cleaning products (such as scouring powder, floor detergents and other household detergents, window-cleaners, etc.), plant- and animal-derived adhesives, synthetic adhesives, welding fumes, vibrations, and contact with animals. Jobs were classified according to the International Labour Office (ILO) classification[18].

At the first stage of analysis, likelihood of exposure to products was evaluated by an expert based on the subject's occupational history. Next, 2 different conclusions (i.e., that of the expert and that of the subject) were compared. If the expert's did not agree with subject's, the case was discussed by the whole team and likelihood of exposure was either confirmed or ruled out.

Statistical analysis. Statistics were compiled using STATA software. After a descriptive analysis of jobs and exposures (of both cases and controls) with chi-square testing, variables were broken down into groups. Jobs were grouped together on the basis of common exposure risks and tasks; jobs with similar rather than identical variables were thus grouped since the original number of different jobs was very high, and the number of workers in each was low.

Two different types of exposure variable were derived.

Cumulative exposure index. The index is defined by Siemiatycki[19] as: $\text{Frequency}_i \times \text{Intensity}_i \times \text{Duration}_{i\ (\text{in years})}$, with frequency for a job_i as: 1 = less than 20% of time exposure in a working week; 2 = 20% to 50%; and 3 > 50%); and intensity as one of 3 semiquantitative levels. This index was divided by experts into 3 different categories following safety criteria (not statistical criteria), namely high, moderate, and low exposure on the basis of the index frequency table (which includes both cases and controls). In the following, the cumulative exposure index is referred to as low, moderate or high when dealing with this type of data.

Levels of exposure. The second exposure variable classified daily exposure into 3 categories: high exposure = 5 or more years of intense exposure (i.e., $\text{Frequency}_i > 2$ and $\text{Intensity}_i > 2$); low exposure = less than 5 years of low-level exposure ($\text{Frequency}_i = 1$ or $\text{Intensity}_i = 1$); moderate exposure = 5 or more years of low-level exposure or less than 5 years of intense exposure.

These variables were created prior to statistical analysis of the data to study exposure levels stipulated by experts rather than to maximize significant differences.

Statistics were analyzed by conditional logistical regression: when there were fewer than 5 cases of SSc, analysis was carried out on the entire population (adjusted for sex and education level), and then by sex according to a single binary variable: yes/no. When there were at least 5 cases, the sexes were separated for logistic regression analysis based on exposure category (low, moderate, or high cumulative exposure index on the one hand, and low, moderate or high exposure level on the other), adjusted for education level. The same analysis was performed for cases restricted to early SSc, to investigate these patients specifically. Finally, an analysis was carried out by entering the most important variables together to explore the hierarchy for the different associations. Results are expressed as odds ratios (OR) with 95% confidence intervals (95% CI). A chi-square test for trend was performed for all variables that might be related to dose (using mean values for each cumulative exposure index category).

RESULTS

Ninety-three cases [10 men (mean age 54.2 yrs), 83 women (mean age 55.4 yrs)] and 206 controls [40 men (mean age 53.1), 166 women (mean age 54.2 yrs)] were included in the survey. As the adult population in the 2 geographical regions has been estimated as 1,004,307, the incidence may be estimated as 9 cases per 100,000 inhabitants over these 5 years and close to 2 per 100,000 inhabitants annually. Clinical classification of cases is shown in Table 1. No significant differences emerged between cases and controls in terms of family situation, ethnic group, or type of residence. The education level of the female controls was significantly higher (p = 0.03) than that of the female cases.

Analysis of jobs. Subjects had an average of more than one job in the course of their professional lives: men [cases: 3.6 (95% CI: 2.1-5.1); controls: 3.3 (2.7-3.9)]; women [cases: 3.0 (2.5-3.4); controls 2.5 (2.2-2.8)]. A detailed job-list for cases and controls is presented in Table 2: construction workers had a significantly higher risk of SSc (OR = 4.01, 95% CI 1.1-14). Several other jobs (teachers, commercial travellers, technicians, cleaning women, and typographers) were also more common among the cases, but not to a significant extent.

Analysis of exposure as determined by experts. Table 3 (cumulative exposure index) and Table 4 (exposure level) show the OR for occupational exposure. Several exposures were significantly (or border-line) associated with SSc, although no clear dose-response effects were observed for any of the indices (no test for trend gave a significant result).

Solvents (low cumulative exposure index) were linked to SSc (OR = 4) in both men and women, although there was no evidence of any dose-response effect. Among all the solvents, halogenated solvents give the highest OR for low cumulative exposure index and moderate exposure level. The OR results for benzene, toluene, and xylenes (BTX) were over 1 but not statistically significant. It is difficult to draw any conclusion about aliphatic solvents because the exposed population was too small.

The incidence of SSc was higher in those who regularly used cleaning products: there was a significant relationship with low cumulative exposure index and moderate exposure level for women alone and both sexes together. OR associated with disinfectants were greater than 1, but none reached significance; the same people exposed to disinfectants were often also exposed to cleaning products and formaldehyde.

Synthetic adhesives were associated with an elevated significant OR in men only, but due to the small number of cases interpretation of analyses could not provide more details. More than 50% of those exposed to abrasive products encountered them in the course of cleaning work. This exposure was almost exclusive to women among whom the incidence of SSc was markedly higher (OR = 2). Duration of exposure was more important than intensity, but the test for trend for duration was not significant (p = 0.10). Exposure to vibration seemed to predispose men to SSc: OR = 3.91, 95% CI 0.8-18, but the small size of the population precludes the possibility of high-resolution analysis to investigate the dose-response relationship (p > 0.10). Exposure so silica dust was not related to SSc. Occupational contact with animals mainly corresponded to agricultural or laboratory work. The increased OR associated with low cumulative exposure index in women was not significant.

No conclusions could be drawn with respect to any other forms of occupational exposure (dyes, pesticides, welding fumes), due to the small size of the exposed populations.

Finally, it should be noted that none of the survey subjects (neither cases nor controls) had ever been exposed to monomeric vinyl chloride, and none of the cases had ever been exposed to epoxy resin. When examining the different exposures together, solvents and cleaning products remained with higher significant OR. When only subgroups of early SSc were considered (26 cases), OR for exposure to solvents and cleaning products were higher in this subgroup than in total sample [OR = 6.04 (1.7-20.7) vs 3.3 ([1.5-6.6) and OR = 3.1 [1.26-7.5] vs 1.8 [0.9-3.5], respectively). An excess of risk remained non-significant for synthetic adhesives, halogenated solvents, and pesticides [OR =

Table 1. Clinical classification of the 93 cases.

Scleroderma Subsets	Criteria	n
Diffuse scleroderma	ACR criteria with proximal skin sclerosis	13
Limited scleroderma	2 of the 3 minor ACR criteria	31
Raynaud's phenomenon	Sclerodactyly	21
+ 1 minor criterion	Pitting scars	2
Raynaud's phenomenon and	Pulmonary fibrosis (chest radiograph)	1
	(1) capillaroscopic "scleroderma pattern"; (2) anticentromere,	3
	antitopoisomerase I, or antinucleolar antibodies	6
	(1) + (2)	16

Table 2. Odds ratios (OR) and 95% confidence levels (95% CI) for SSc relative to occupation (adjusted for sex and education level).

Job	Cases, n (%)	Controls, n (%)	OR	95% CI
Farmers	7 (7.5)	18 (8.7)	0.5	0.2–1.5
Domestic workers				
Cleaners	28 (30.1)	38 (18.4)	1.4	0.7–2.7
Cooks	7 (7.5)	12 (5.8)	1.1	0.4–3.1
Managers and executives	4 (4.3)	17 (8.3)		
Commercial travellers	22 (23.7)	32 (15.5)	1.4	0.7–2.7
Teachers	12 (12.9)	24 (11.7)	2.5	0.9–7.1
Office workers	31 (33.3)	79 (38.3)	0.7	0.3–1.2
Other services	2 (2.2)	6 (2.9)		
Technicians	4 (4.3)	7 (3.4)	1.8	0.4–7.0
Nurses	2 (2.2)	7 (3.4)	1.1	0.2–5.8
Nursing auxiliaries and child-minders	9 (9.7)	17 (8.3)	0.9	0.3–2.2
Warehouse workers	1 (1.1)	10 (4.9)		
Engineers	0	3 (1.5)	—	—
Hair stylists and beauty parlor workers	3 (3.2)	7 (3.4)	0.9	0.2–3.6
Construction workers	9 (9.7)	11 (5.3)	4.0	1.1–14.0
Metal workers	0	10 (4.9)	—	—
Mechanics	2 (2.2)	14 (6.8)	0.3	0.0–1.4
Fabric and leather workers	7 (7.5)	17 (8.3)	0.6	0.2–1.7
Chemical plant workers	1 (1.1)	5 (2.4)		
Paper industry workers	2 (2.2)	5 (2.4)		
Typographers and photographic workers	3 (3.2)	2 (1.0)	5.4	0.8–35.7
Food processing workers	2 (2.2)	2 (1.0)		
Machine operators	3 (3.2)	3 (1.5)		
Assembly workers	3 (3.2)	16 (7.8)		

4.72; (0.76-29.29)]. In fact, it was not possible to thoroughly study this relationship due to the small sample size.

DISCUSSION

Most epidemiological studies addressing the etiology of SSc follow a case control design because of the low disease prevalence. However, one historical cohort study has been conducted in Sweden[20]: in this study, hospital registry data were correlated with a job-exposure matrix (based only on the most recent job). The innovative feature of our survey is that it was conducted in near-perfect conditions by an experienced clinical investigation center (and its team of experts) in close conjunction with a regional SSc registry and a group of occupational health specialists with expertise in retrospective analysis of occupational exposure patterns[21]. The existence of the regional SSc registry made it possible to select controls from the general population: this precludes selection bias that can result from using controls selected from hospital patients.

Patient population characteristics covered by our survey were fully comparable to those in the literature: the ratio of women to men was 8.3 compared to between 1.8 and 15 in the various published studies[1,2]. The mean age at which the disease was diagnosed was 52.7 ± 13.6 for the men, and 54 ± 13.5 for the women (compared to between 40 and 50[22]). Typical antibodies were detected in 92.47% of the cases (compared with published figures of between 80 and 95%[22]).

Statistical power was a problem although our sample sizes were comparable to others (Table 5). The decision to use experts to define exposure levels (low, moderate, or high) based on objective criteria reduced the size of the high exposure population, making it impossible to carry out certain analyses, particularly dose-response analysis. An alternative approach would have been to divide the exposure ranges into tertiles which would have insured a greater number of subjects in the high-exposure group. However, this approach would not have been an accurate representation of the real situation.

To enhance statistical power, 4 controls were selected for each man (heavy female predominance of SSc) but in spite of this strategy, it was not possible to study exposure levels among the men.

The results show significant OR for exposure to solvents in both men and women. Most previous studies (Table 5) similarly detected a relationship between solvent exposure and SSc (apart from one conducted on a smaller population[23]). Garabrant[11] specifically inculpated mineral spirits, naphtha, and white spirits and detected significant OR with self-reported exposure (OR = 1.5, 95% CI 1.1-2.0) not con-

Table 3. Odds ratio (OR) and 95% confidence limit (95% CI) associated with exposure to various products or families of products as measured by the cumulative exposure index (adjusted for education level).

Products	Total Population*				Women				Men			
	n_1	n_2	OR	95% CI	n_1	n_2	OR	95% CI	n_1	n_2	OR	95% CI
Solvents (in general) (yes/no)	28	35	3.2	1.5–6.6	19	17	2.8	1.2–6.1	9	18	8.4	0.9–78.6
Level 1–48	26	31	4.0	1.8–8.6	18	15	3.2	1.4–7.2	8	16	41.8	0.8–319.4
Level > 48	2	4	0.7	0.1–4.0	1	2	0.6	0.0–7.3	1	2	3.3	0.1–95.1
Halogenated solvents (yes/no)	12	21	2.5	0.8–7.3	5	6	1.8	0.5–6.6	7	15	6.2	0.6–64.2
Level 1–45	10	16	3.0	0.9–9.9								
Level > 45	2	5	1.4	0.2–9.3								
BTX (yes/no)	10	19	1.3	0.5–3.2	6	8	1.3	0.4–3.8	4	11	1.4	0.3–6.5
Level 1–12	7	10	1.7	0.7–4.1								
Level 12–40	3	9	—									
Aliphatic solvents (yes/no)	2	2	1.4	0.2–9.7								
Cleaning products	32	43	1.6	0.9–3.0	32	43	1.7	0.9–3.2				
Level 1–33	23	28	1.8	0.9–3.5	23	27	1.8	0.9–3.6				
Level > 33	9	15	1.3	0.5–3.3	9	15	1.3	0.5–3.4				
Disinfectants	9	13	2.0	0.7–5.3	9	11	2.3	0.8–6.5				
Level 1–33	7	9	2.0	0.6–6.4	7	8	2.5	0.7–8.5				
Level > 33	2	4	1.9	0.3–11.9	2	3	1.9	0.3–12.2				
Formaldehyde	8	13	1.5	0.6–3.9	7	9	1.7	0.6–5.0				
Level 1–29	3	7	0.9	0.2–4.0	2	4	0.9	0.1–2.5				
Level > 29	5	6	2.1	0.6–7.3	5	5	2.5	0.7–9.3				
Synthetic adhesive (yes/no)	4	4	3.5	0.8–15					3	1	25.3	1.3–472
Vibration (yes/no)	6	12	1.8	0.5–5.8					5	8	3.9	0.8–19
Silica dust (yes/no)	4	13	0.9	0.2–3.2					4		0.9	0.2–4.4
Level 1–38	3	10	0.8	0.2–3.4								
Level > 38	1	3	1.2	0.1–12								
Abrasive products	16	21	1.6	0.7–3.4	15	14	1.9	0.8–4.3				
Level 1–10	9	13	1.3	0.5–3.4	9	9	1.7	0.6–4.8				
Level > 10	7	7	2.1	0.7–6.2	6	5	2.3	0.6–7.9				
Animal contacts	12	17	1.3	0.5–3.1	11	14	1.4	0.5–3.4				
Level 1–72	7	8	2.0	0.6–7.0	7	5	2.7	0.7–10.2				
Level > 72	5	9	0.9	0.2–2.9	4	9	0.7	0.2–2.6				
Dyes (yes/no)	3	3	2.0	0.3–10.5	3	3	2.0	0.3–10.5				
Pesticides (yes/no)	3	4	1.7	0.3–8.4								
Welding fumes (yes/no)	2		0.5	0.1–2.4								

n_1: number of exposed scleroderma, n_2: number of exposed controls, BTX: benzene, toluene, xylene. * Adjusted for sex and education.

firmed by expert reviewed exposure. In another study, Diot[8] detected significant OR for a number of categories of solvents: chlorinated solvents, OR = 2.61 (1.20-5.66); aromatic solvents, OR = 2.67 (1.06-6.67), and also for certain specific products: white spirit, OR = 3.46 (1.48-8.11), toluene, OR = 3.44 (1.09-10.90), and trichloroethylene, OR = 2.39 (1.04-5.22).

The significance of OR values detected in all these studies warrants recognition of SSc as an occupational disease due to exposure to solvents. Cleaning products, which may include solvents, were characterized by experts and were related to disease in women. This was compatible with analysis of different jobs, and identifies cleaning workers as being at particularly high risk. Exposure to synthetic adhesives was related to SSc and this association should be further evaluated. Construction work, also associated with SSc, is another type of job in which there is regular exposure to both solvents and cleaning products. No other form of occupational exposure seemed to be a significant risk factor for the disease.

Exposure to silica dust was not found to be a significant risk factor in this study despite the OR of 1.2 for high exposure. Although this risk is well documented in some recent case control studies[8,24], others have failed to find a statistically significant relationship[7,14,25] because of relatively low prevalence of exposures in women and difficulty in evaluating full occupational history. We found a trend indicating a disease association with exposure to abrasive products (that commonly contain silica) although it did not quite achieve significance. The link between vibration and SSc is difficult to investigate because vibration is often associated with exposure to silica dust (e.g., when sanding surfaces)[26,27].

In conclusion, our case-control study confirms the importance of certain forms of occupational exposure in the development of SSc and early SSc, specifically exposure to solvents in both men and women, as well as exposure to clean-

Table 4. Odds ratio (OR) and 95% confidence limit (95% CI) associated with exposure to various products or families of products as calculated on the basis of 3 different levels of exposure, overall population and women alone* (adjusted for sex and education level).

Products	Total Population n_1	n_2	OR	95% CI	Women n_1	n_2	OR	95% CI
Solvents (in general)								
Low level	8	4	16.8	3.0–94	7	1	17.7	2.13–14.2
Moderate	16	27	2.3	0.9–5.4	9	14	1.5	0.5–4.0
High	4	7	1.4	0.3–5.7	3	2	2.0	0.3–13.4
Halogenated solvents								
Low level	1	1	6.3	0.2–175.8			—	
Moderate	9	15	3.5	0.9–13.1				
High	2	5	1.0	0.1–6.4				
BTX								
Low level	4	5	1.7	0.4–6.6			—	
Moderate	6	11	1.5	0.4–5.0				
High	0	3						
Cleaning products								
Low level	8	10	1.7	0.6–4.7	8	10	1.7	0.6–4.8
Moderate	18	19	2.2	0.9–5.1	18	18	2.3	1.0–5.6
High	6	14	0.8	0.3–2.5	6	14	0.9	0.3–2.5
Disinfectants								
Low level	3	3	2.5	0.4–13.6	3	2	3.5	0.5–22.7
Moderate	4	7	1.6	0.3–6.8	4	6	1.7	0.4–7.7
High	2	3	2.1	0.3–14.1	2	3	2.2	0.3–14.8
Formaldehyde								
Low level	3	5	1.5	0.3–7.5	2	2	1.9	0.2–14.6
Moderate	1	6	0.3	0.0–3.3	1	5	0.4	0.0–3.9
High	4	2	6.0	0.9–36.7	4	2	6.3	1.0–39.5
Synthetic adhesive								
Low level	0	2					—	
Moderate	4	2	6.7	1.1–40.3				
Silica dust								
Low level	0	2						
Moderate	3	8	1.0	0.2–4.0			—	
High	1	3	1.2	0.1–11.6				
Abrasive products								
Low level	4	7	1.2	0.3–4.9	4	3	1.9	0.4–9.1
Moderate	11	10	1.7	0.7–4.4	11	9	2.1	0.8–5.5
High	1	3	0.9	0.1–9.7	0	1	—	
Animals								
Low level	0	1						
Moderate	4	3	5.87	0.5–61.6			—	
High	8	13	1.08	0.4–2.8				

* Since the male populations were so small, exposure level analysis was not performed. n_1: number of exposed scleroderma, n_2: number of exposed controls, BTX: benzene, toluene, xylene.

ing products. The consistency in our findings with other studies warrants recognition of the occupational nature of the disease, and should incite immediate action to improve preventive measures.

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Table 5. Previous occupational case-control studies.

Toxin	Study	Cases/Controls, n	OR	95% CI
Silica dust	Bovenzi[7]	21/42	2.1	0.3–13.6
	Burns[14]	274/1184	1.5	0.7–2.9
	Diot[8]	80/160	**5.5**	**1.6–18.3**
	Bovenzi[25]	55/171	1.7	0.4–7.6
	Englert[24]	160/83	**1.8**	**3.9–8.5**
Solvents	Silman[23]	56/56	1.3	0.6–2.7
	Bovenzi[7]	21/42	**9.2**	**1.0–243.8**
	Schaeverbeke[10]	51/165	**5.5**	**1.2–25.0**
	Goldman[9]	33/246	**5.8**	**2.3–14.4**
	Nietert[28]	178/200	**2.9**	**1.1–7.6**
	Diot[8]	80/160	**2.6**	**1.3–5.2**
	Garabrant[11]	623/2129	**2**	**1.5–2.5**
	Aryal[29]	Metaanalysis	**3.14**	**1.5–6.3**
	Bovenzi[25]	55/171	**2.3**	**1.0–5.4**
Epoxy resins	Silman[23]	56/56	1.7	0.4–7.3
	Diot[8]	80/160	**4.2**	**1.0–17.4**
Formaldehyde	Silman[23]	56/56	0.8	0.2–3.0
Mineral spirits, naphtha, white spirits	Garabrant[11]	623/2129	**1.5**	**1.1–2.0**
Hair dyes	Freni-Titulaer[12]	44/88	**7.2**	**1.9–26.9**

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