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# Thèse

Pour le

## DOCTORAT EN MEDECINE

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par


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**TITRE**

L'EXPOSITION OCCUPATIONNELLE EST INDEPENDAMMENT ASSOCIEE AU DECLIN DE LA CAPACITE VITALE FORCEE CHEZ LES HOMMES ATTEINTS DE SCLERODERMIE SYSTEMIQUE: ETUDE DE COHORTE RETROSPECTIVE

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# L'EXPOSITION OCCUPATIONNELLE EST INDEPENDAMMENT ASSOCIEE AU DECLIN DE LA CAPACITE VITALE FORCEE CHEZ LES HOMMES ATTEINTS DE SCLERODERMIE SYSTEMIQUE: ETUDE DE COHORTE RETROSPECTIVE


**Résumé**

**Objectif**: Le genre masculin et l'exposition occupationnelle (EO) aux substances toxiques sont des marqueurs de mauvais pronostic dans la Sclérodermie Systémique (ScS). L'objectif était d'évaluer l'impact respectif du genre et de l'EO sur les caractéristiques des patients atteints de ScS et sur la variation de la capacité vitale forcée (CVF) et de la capacité de diffusion du monoxyde de carbone corrigée par l'hémoglobine (DLCOc).

**Méthodes**: Les patients atteints de ScS avaient une évaluation quantitative de l'EO via un score cumulatif d'exposition (SCE). L'association entre le SCE et les caractéristiques était explorée chez 210 patients. L'association entre le SCE et la variation de la CVF et de la DLCOc était évaluée chez 144 patients avec ≥4 mesures de la fonction pulmonaire sur ≥1 an, via des modèles uni et multivariés.

**Résultats**: Le genre masculin était associé à l'EO (OR =10,3 [IC à 95% 5,1-21,9], p <0,0001). Le SCE était plus élevé chez les patients atteints de forme diffuse que limitée. Le SCE était indépendamment associé à la variation annuelle de la CVF au cours du temps, en particulier chez les hommes (p = 0,03), à une baisse de la CVF ≥10% par rapport à la base (p = 0,01), et inversement corrélé avec la variation annuelle de la CVF (R2 = -,33, p <0,0001). La prévalence de la pneumopathie interstitielle diffuse était similaire selon le genre ou le statut d'exposition.

**Conclusion**: L'EO est indépendamment associé au déclin de la CVF avec une relation dose-effet, mais pas au déclin de la DLCOc ou de la maladie pulmonaire interstitielle. L'évaluation de l'exposition correspond à un outil d'évaluation pronostique de la ScS. L'éviction de l'exposition professionnelle devrait être une priorité dans la ScS.

# OCCUPATIONAL EXPOSURE IS INDEPENDENTLY ASSOCIATED WITH DECLINE OF FORCED VITAL CAPACITY IN MALES WITH SYSTEMIC SCLEROSIS: A RETROSPECTIVE COHORT STUDY


## Abstract

**Objective**: Male gender and occupational exposure (OE) to toxicants are markers of poor prognosis in Systemic Sclerosis (SSc). To assess the respective impact of male gender and OE on SSc patients' characteristics and variation in forced vital capacity (FVC) and the hemoglobin-corrected transfer coefficient for carbon monoxide in the lung (DLCOc).

**Methods**: Patients with SSc underwent quantitative assessment of OE through a cumulative exposure score (CES). Association of the CES with baseline characteristics was explored in n=210 patients. Association of the CES with variation of FVC and DLCOc over time was assessed in n=144 patients with ≥4 lung function measurements over ≥1 year, through univariate and multivariate models.

**Results**: Male gender strongly associated with exposure (OR [95%CI]=10.3 [5.1-21.9], p<0.0001). The CES was higher in patients with diffuse SSc compared to limited SSc. The CES independently associated with yearly variation of FVC over time (p<0.03), particularly in male gender (p=0.03), and correlated inversely with yearly variation of FVC ($R^2$= -.33, p<0.0001), and independently associated with the occurrence of a FVC decline ≥10% from baseline (p=0.01). By contrast, the CES did not associate with yearly variation in DLCOc or DLCOc decline ≥15%. The prevalence of interstitial lung disease was similar across gender or OE status.

**Conclusion**: The OE independently and dose-dependently associated with decline of FVC, but not with decline of DLCOc or interstitial lung disease. Assessment of OE provides a tool for SSc prognostication. Avoidance of OE should be a high priority in SSc.



**Mots clés**: Sclérodermie Systémique, Genre, Exposition occupationnelle, Déclin de la CVF

**Keywords**: Systemic Sclerosis, Gender, Occupational exposure, FVC decline

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je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

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# Abréviations

- ACR/EULAR: ACR/European League Against Rheumatism
- Topo I Ab: anti-Topoisomerase I/Scl70 antibodies
- CES: cumulative exposure score
- dcSSc: diffuse cutaneous form
- DLCO: diffusing capacity of the lungs for carbon dioxide
- %pDLCOc: percent predicted hemoglobin-corrected transfer coefficient for carbon monoxide
- FVC: forced vital capacity
- %pFVC: percent predicted forced vital capacities
- GIT: gastrointestinal tractus involvement
- HRCT: high-resolution computed tomography scan
- ILD: interstitial lung disease
- PAH: pulmonary arterial hypertension
- PFT: pulmonary function test
- sPAP: systolic pulmonary artery pressure
- SSc: systemic sclerosis
- SSc-ILD: SSc-related interstitial lung disease
- TTE: transthoracic echocardiogram
- WHO: world health organization
- 6MWD: six-minute walk distance

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# 1. Introduction

Systemic sclerosis (SSc) is a multifactorial systemic disease causing fibrosis and vessel obliteration in affected organs (1).

Reduced lung function is frequent in patients with SSc (2–4) and is associated with poor outcomes (5,6). Lung function is explored by measuring lung volumes, typically forced vital capacity (FVC), and pulmonary gas exchange, primarily the diffusing capacity of the lungs for carbon dioxide (DLCO) (2,7). FVC can be reduced by changes in lung compliance, airway obstruction, chest wall compliance or reduced respiratory muscle strength, while alveolar lesions or pulmonary vascular disease can reduce DLCO. In patients with SSc, interstitial lung disease (SSc-ILD) can reduce lung compliance, extensive skin fibrosis may reduce chest wall compliance (8), and chest wall muscle atrophy might reduce respiratory muscle strength (9), while pulmonary gas exchange can be altered by SSc-associated interstitial lung disease (SSc-ILD), pulmonary arterial hypertension (PAH), or cardiac disease.

Occupational exposure to toxic compounds is a key risk factor of developing SSc (10). This is strongly demonstrated, especially concerning crystalline silica, solvents and epoxy resins (10). Occupational exposure is more frequent in male than in female SSc patients (11,12). Occupational exposure may be associated with specific organ involvement and poor outcomes (13). In particular, it has been claimed that occupational exposure may be associated with a higher risk of developing SSc-ILD, extensive skin fibrosis (13), and myopathy (14).

Although determinants of SSc severity are poorly understood, male gender is consistently associated with poor prognosis in SSc. Indeed, male gender is associated with the diffuse cutaneous form (dcSSc), visceral involvement (13,12), and worse survival in SSc (15). Whether male gender is a risk factor for SSc-ILD and accelerated lung function decline, however, is controversial (16,17). Because there is a strong association between male gender and occupational exposure, the respective

weight of gender or occupational exposure on the occurrence, affected organs, and outcome of SSc is very difficult to assess.

The objective of this study was to assess the respective impact of male gender and occupational exposure on patient characteristics and progression of lung function over time in a cohort of patients with SSc who underwent systematic assessment of occupational exposure. In particular, we explored 1) whether there was a dose-dependent relationship between occupational exposure and lung function decline in patients with SSc, and 2) whether male gender and occupational exposure were independently associated with lung function decline in multivariate models.

# 2. Patients and Methods

## 2.1. Study design and study population

A single-center retrospective study was conducted at the rare diseases center of a tertiary care university hospital in Tours, France. All patients with a physician diagnosis of SSc between January 1st, 1999 and December 31st, 2018 were considered for inclusion in the study. Patients were included if they, 1- had a diagnosis of SSc according to the 1980 ACR or ACR/EULAR criteria (18,19) (**Annex 1**), 2- were more than 18 years of age at inclusion, 3- had at least one pulmonary high-resolution computed tomography scan (HRCT) and 4- had at least one pulmonary function test (PFT) including spirometry and carbon monoxide transfer (DLCO) measurements, and 5- did not fulfill diagnostic criteria for other systemic auto-immune diseases. More than 4 PFTs and at least one year of follow-up were required for the analysis of correlations between occupational exposure and decline of FVC and DLCOc, to allow the calculation of annual changes in FVC and DLCOc. All patients gave written consent to be included in retrospective clinical studies. Approval of the local Ethics Committee was obtained (“Espace de Réflexion Ethique Région Centre” research project n° 2018-096).

## 2.2. Patient characteristics

All data were obtained retrospectively from clinical records to provide structured clinical case reports at the time of initial diagnosis and at the time of the last evaluation. Data included age at diagnosis, duration of disease from onset of the first symptom other than Raynaud's phenomenon, PAH (defined by mean pulmonary arterial pressure ≥25 mmHg and pulmonary artery wedge pressure ≤15 mmHg, measured by right heart catheterization) (20), occurrence of SSc-ILD, clinical form of disease (limited SSc or diffuse SSc) according to Leroy's criteria (21), calcinosis, digital ulcers, a physician's diagnosis of muscle weakness, nailfold capillaroscopic abnormalities, and gastrointestinal, cardiac or renal manifestations of SSc. Immunological status was specified (anti-centromeres and/or anti-Scl70 antibodies).

## 2.3. Pulmonary function tests

PFTs performed at the time of SSc diagnosis, along with all subsequent PFTs, were reviewed. Forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV1) were obtained by spirometry. Total lung capacity (TLC) was obtained by plethysmography. DLCO was measured by the single-breath test and was corrected for hemoglobin (DLCOc) according to ATS/ERS guidelines (22,23). Percentage predicted (%p) values were calculated (%pFEV1, %pFVC, %pTLC, %pDLCOc) according to ECCS1993 equations (24). PFTs were performed using Sensormedics (before 2015) and Jaeger (from 2015) equipment.

## 2.4. ILD assessment

For each patient, the last available HRCT was analyzed by a radiologist with expertise in ILD, blinded to clinical status and occupational exposure. SSc-ILD was defined by the presence of a reticular pattern and/or ground-glass opacification and/or traction bronchiectasis and/or honeycombing, and stratified according to Goh's classification (25) (**Annex 2**).

## 2.5. Assessment of occupational exposure

All subjects had a 30-min interview with a trained industrial hygienist and occupational practitioner who was blinded to clinical status. The interview was based on a structured

questionnaire used in previous studies in SSc and primary Sjögren's syndrome (26–28) (**Annex 3**). The questionnaire included socioeconomic and personal characteristics, and complete occupational histories, including exposure to crystalline silica dust, silicon, vinyl chloride, welding fumes, solvents (chlorinated and aromatic solvents, white spirit and other hydrocarbons, ketones), epoxy resins, pesticides, and. lifestyle activities (e.g., gardening, do-it-yourself). Patients were questioned about potential confounding factors such as silicone implants, cosmetic surgery, and hair dyeing. Exposure assessments were semi-quantitative, based on the expert's knowledge of industrial processes. Any work period of 6 months or more was recorded.

For each occupational period, probability (probability score of 0 = non-exposure, 0.25 = possible exposure, 0.75 = probable exposure, and 1 = certain exposure), duration (number of years), intensity (intensity score from 0 for non-exposure to 4 for highest level of exposure) and frequency (with a frequency score based on length of time worked daily: <10% = 0.05, 10-50% = 0.30, and >50% = 0.75) of exposure were determined for each toxic agent. The cumulative exposure score (CES) for each employment period was expressed as probability x duration x intensity x frequency. The CES for a given subject was expressed as the sum of employment exposure scores for all periods of employment.

## 2.6. Statistical analysis

Continuous variables were expressed as median (interquartile range-IQR) or mean ± standard deviation (SD), and were compared with the Mann-Whitney U-test or Student's t.test, depending on distribution assessed by Shapiro's test. Categorical variables were described as total and proportion (%), and were compared by Fisher's exact test. Occupational exposure was analyzed as a continuous variable with the CES (26–28).

We evaluated associations between gender and occupational exposure (as a qualitative variable) through logistic regression with calculation of odd ratios (OR [95% Confidence Intervals

CI]), then between CES (as a continuous variable) and patient characteristics. Next, to determine whether occupational exposure predicted variations in FVC (mL/year and %predicted/year) and DLCOc (mL/min/mmHg/year and %predicted/year) over time, we used three methods.

First, annual variations in FVC and DLCOc were calculated by linear regression. To identify the predictor factors of annual FVC or DLCOc variation, univariate and multivariate linear regression models were used. Parameters were included in multivariate models if the p-value was <0.2 in univariate models. Follow-up time, smoking, clinical form of SSc, SSc-ILD, and positivity of anti-Scl70 antibodies were used as confounding factors (29). PAH or presence of digital ulcers were added for the progression of DLCOc over time (17). Correlations between the CES and decline in FVC or decline in DLCOc were explored by their regression slopes and Pearson correlation coefficient ($R^2$). We then restricted analysis on gender and specific toxicants.

Second, we assessed the potential predictor factors associated with decline in FVC ≥10% from baseline or DLCOc ≥15% from baseline with the same method of uni- and multivariate regression, including gender or CES.

Third, variations in FVC and DLCOc were treated by calculating the time needed for FVC to decline ≥10% from baseline, or for DLCOc to decline ≥15%, using a Cox regression model with log-rank test, with adjustment on follow-up delay. We compared the proportion of patients in whom SSc-ILD occurred by Fisher's exact test.

A p-value (p) of <0.05 was considered statistically significant. Data were analyzed by BT, using R software, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). The study was developed, and the results are reported according to the guidelines on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (30).

# 3. Results

## 3.1. Patients

A total of two hundred and forty-seven SSc cases were screened for inclusion. Thirteen patients fulfilled the criteria of Mixed Connective Tissue Disease and were not included. Ten patients did not undergo HRCT and 14 patients had no PFTs, and were not included (**Figure 1**). Consequently, 210 patients were analyzed.

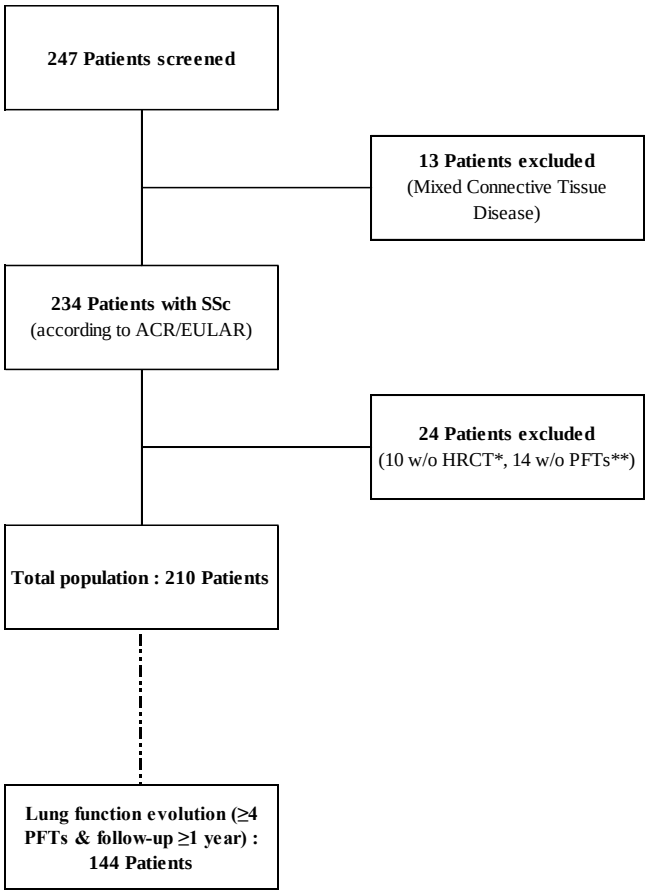


**Figure 1.** Flowchart of Sclerogenre study

*High-Resolution Computed Tomography (HRCT) not found in clinical record, **Baseline Pulmonary Function Tests (PFTs) not found in clinical record. American College of Rheumatology (ACR) criteria of ACR/European League Against Rheumatism (ACR/EULAR) criteria; Systemic Sclerosis (SSc)

The study population comprised 55 men (26.2%) and 155 women (73.8%). Baseline characteristics of patients, at the start of follow-up, are reported in **Table 1**. Males were slightly younger (median 62 versus 66 years). Age at SSc onset did not differ between genders. Follow-up was shorter in males (9.1±8.4 *vs.* 12.1±8.9 years). Diffuse cutaneous SSc was more frequent in males (50.9%) than in females (26.5%). SSc-related heart disease was found in 25% of males and 11% of females (p=0.01), while gut and kidney involvement were similar in both genders. Immunosuppressive therapies were more frequent in males. Males were also more likely to have a history of smoking (63.6 *vs*. 24.5%). At baseline, in the overall population, %pFVC and %pDLCOc didn't differ according to gender (both p>0.05).

Over the course of follow-up, SSc-ILD was diagnosed in 92/210 (43.8%) patients overall, with similar frequency in males (47.3%) and females (42.6%). The delay between SSc diagnosis and ILD onset was 4±7 years and didn't differ between genders. Likewise, no significant gender-related difference was noted regarding radiological patterns and the extent of infiltrative involvement. Extensive lung fibrosis was found on HRCT in 36.4% of men and 27.1% of women (p>0.05) (**Tables 1** & **2**).

**Table 1.** Baseline characteristics of all patients

| | All patients N=210 | Male N=55 | Female N=155 | P-value |
|---|---|---|---|---|
| **Clinical characteristics** | | | | |
| Age (years), median (IQR) | 65 (54-74) | 62 (53-69) | 66 (54-76) | **0.0461** |
| Diffuse SSc subset, n(%) | 69 (32.7) | 28 (50.9) | 41 (26.5) | **0.0013** |
| Age at SSc onset (years), median (IQR) | 51 (41-62) | 54 (41-60) | 51 (41-63) | 0.9546 |
| Delay between Raynaud phenomenon and diagnosis (years) mean±SD | 7.4±11.4 | 6.3±9.7 | 7.8±12.0 | 0.6183 |
| Follow-up period (years), mean±SD | 11.9±8.9 | 9.1±8.4 | 12.9±8.9 | **0.0023** |
| Sclerodactylia, n(%) | 195 (92.4) | 52 (94.5) | 142 (91.6) | 0.5210 |
| Digital ulcer/pitting scars, n(%) | 122 (57.1) | 37 (67.3) | 85 (54.8) | 0.1108 |
| Calcinosis, n(%) | 62 (29.0) | 13 (23.6) | 48 (31.0) | 0.3005 |
| Nailfold capillaroscopic abnormalities, n(%) | 149 (70.5) | 37 (67.3) | 111 (71.6) | 0.5056 |
| Gastroesophageal reflux, n(%) | 159 (75.7) | 39 (70.9) | 120 (77.4) | 0.3572 |
| | | | | |
| **Exposition features** | | | | |
| Occupational exposure, n(%) | 79 (37.6) | 42 (76.4) | 37 (23.9) | **<0.0001** |
| Cumulative exposure score, mean±SD | 8.0±18.6 | 22.5±28.2 | 2.9±9.3 | **<0.0001** |
| Crystalline silica exposure, n(%) | 30 (14.3) | 23 (41.8) | 7 (4.5) | **<0.0001** |
| Chlorinated solvent, n(%) | 53 (25.2) | 29 (52.7) | 24 (15.5) | **<0.0001** |
| Aromatic solvents, n(%) | 16 (7.6) | 10 (18.2) | 6 (3.9) | **0.0015** |
| Hydrocarbons exposure, n(%) | 17 (8.1) | 10 (18.2) | 7 (4.5) | **0.0030** |
| Formaldehydes exposure, n(%) | 9 (4.3) | 3 (5.5) | 6 (3.9) | 0.6999 |
| Epoxy resins, n(%) | 23 (11.0) | 18 (32.7) | 5 (3.2) | **<0.0001** |
| Welding fumes, n(%) | 11 (5.2) | 9 (16.4) | 2 (1.3) | **0.0001** |
| Ketones exposure, n(%) | 11 (5.2) | 3 (5.5) | 8 (5.2) | 1 |
| | | | | |
| Tobacco smoking, n(%) | 73 (34.6) | 35 (63.6) | 38 (24.5) | **<0.0001** |
| | | | | |
| **Organs involvements** | | | | |
| *Interstitial lung disease, n(%)* | 92 (43.8) | 26 (47.3) | 66 (42.6) | 0.6355 |
| HRTC Extensive lung fibrosis, n(%) | 62 (29.5) | 20 (36.4) | 42 (27.1) | |
| WHO dyspnea functional III/IV class, n(%) | 36 (17.1) | 12 (21.8) | 24 (15.5) | 0.3010 |
| 6MWD (meters), median (IQR) | 473 (393-551) | 510 (380-577) | 461 (395-539) | 0.2107 |
| First Pulmonary Functional Tests | | | | |
| %pFVC, mean±SD | 102.7±22.1 | 99.0±21.0 | 104.0±22.5 | 0.1606 |
| %pFVC<80%, n(%) | 24 (26.1) | 7 (26.9) | 17 (25.8) | 1 |
| %pDLCOc, mean±SD | 73.0±20.9 | 74.3±18.7 | 72.6±21.7 | 0.6238 |
| %pDLCOc<70%, n(%) | 44 (47.8) | 10 (38.5) | 34 (51.5) | 0.4800 |

| | | | | |
|---|---|---|---|---|
| Patients with ≥ 4 PFTs, n(%) | 144 (68.6) | 37 (67.3) | 107 (69.0) | 0.8092 |
| | | | | |
| *GIT involvement, n(%)* | 159 (75.7) | 39 (70.9) | 120 (77.4) | 0.3572 |
| *PAH, n(%)* | 30 (14.3) | 7 (12.7) | 23 (14.8) | 0.8243 |
| Last sPAP by TTE (mmHg), median (IQR) | 30 (25-40) | 30 (25-35) | 30 (26-37) | 0.7640 |
| *Left heart involvement, n(%)* | 31 (14.8) | 14 (25.5) | 17 (11.0) | **0.0141** |
| *Scleroderma renal crisis, n(%)* | 5 (2.4) | 1 (1.8) | 4 (2.6) | 0.1319 |
| | | | | |
| **Biological features** | | | | |
| Antinuclear antibody, n(%) | 210 (99.5) | 54 (98.2) | 155 (100) | 0.2619 |
| Anticentromere antibody, n(%) | 107 (51.0) | 18 (32.7) | 89 (57.4) | **0.0017** |
| Anti-Scl 70, n(%) | 59 (28.1) | 21 (38.2) | 38 (24.5) | 0.0571 |
| | | | | |
| **Treatments** | | | | |
| Steroids, n(%) | 55 (26.2) | 15 (27.3) | 40 (25.8) | 0.8571 |
| Methotrexate, n(%) | 23 (11.0) | 11 (20.0) | 12 (7.7) | **0.0199** |
| Immunosuppressive therapy | 39 (18.6) | 16 (29.1) | 23 (14.8) | **0.0261** |
| Cyclophosphamide, n(%) | 28 (13.3) | 10 (18.2) | 18 (11.6) | 0.2437 |
| Mycophenolate mofetil, n(%) | 23 (11.0) | 12 (21.8) | 11 (7.1) | **0.0042** |
| Azathioprine, n(%) | 8 (3.8) | 2 (3.6) | 6 (3.9) | 1 |

Legend: High-resolution CT scan (HRCT); Heart dysfunction: pericardial effusion, conduction or rhythm disorder, or myocarditis or dilated myocardiopathy without coronary ischemic disease; gastrointestinal tractus involvement (GIT); Pulmonary functional tests: percent predicted hemoglobin-corrected transfer coefficient for carbon monoxide in the lung (%pDLCOc), percent predicted forced vital capacities (%pFVC) are indicated on for all patients (n=210); six-minute walk distance (6MWD); systolic pulmonary artery pressure (sPAP) by transthoracic echocardiogram (TTE); pulmonary arterial hypertension (PAH); world health organization (WHO); Specific treatment: inhibitor of phosphodiesterase type 5 (IPDE5); standard deviation (SD)

## 3.2. Occupational Exposure

Occupational exposure was found in 79/210 (37.6%) of patients. The most frequent exposures were chlorinated solvents (25.2% of patients), crystalline silica (14.3%), epoxy resins (11.0%), hydrocarbons (8.1%) and aromatic solvents (7.6%) (**Table 1**). Exposure to toxicants was strongly associated with male gender (76.4% of males *vs*. 23.9% of females, Odds ratio [95%CI] of 10.3 [5.1-21.9], p<0.0001), especially for crystalline silica (OR = 15.2 [6.3-41.2]), epoxy resins (OR = 14.5 [5.3-46.6]), and chlorinated solvents (OR = 6.1 [3.1-12.2]). The median number of toxicants

in exposed patients was 3 in males and 1 in females (p<0.01). The cumulative exposure score (CES) was higher in males (22.5±28.2) than in females (2.9±9.3, p<0.0001) (**Table 1**). The cumulative duration of exposure was higher in men (23 *vs*. 11 years, p<0.0001). Duration of exposure for the three main toxic agents was longer in males (p<0.001 for chlorinated solvents and crystalline silica, and p=0.001 for epoxy resins, **Table 2**).

**Table 2.** Specific characteristics of Occupational Exposure and Interstitial Lung Disease according to gender in all patients

| | **All patients N=210** | **Male N=55** | **Female N=155** | **P-value** |
|---|---|---|---|---|
| **Time of exposure (years), mean±SD (n=79)** | | | | |
| **Number of cases at risk, n(%)** | 79 (37.6) | 42 (76.4) | 37 (23.9) | **<0.0001** |
| Cumulative duration (y) | 17±13 | 23±13 | 11±10 | **<0.0001** |
| Silica (y) | 9±14 | 14±17 | 3±8 | **0.0006** |
| Chlorinated solvents (y) | 13±15 | 18±18 | 6±8 | **0.0002** |
| Aromatic solvents (y) | 2±5 | 3±6 | 1±3 | 0.1443 |
| Hydrocarbons (y) | 3±8 | 4±9 | 2±7 | 0.2037 |
| Formaldehydes exposure (y) | 2±7 | 1±6 | 2±8 | 0.4869 |
| Epoxy resin (y) | 6±12 | 10±15 | 2±5 | **0.0017** |
| Welding fumes (y) | 3±9 | 5±12 | 0±1 | **0.0134** |
| Ketones (y) | 2±6 | 1±4 | 3±7 | **0.0017** |
| | | | | |
| **ILD characteristics in total population (n=210)** | | | | |
| **Number of cases at risk, n(%)** | 92 (43.8) | 26 (47.3) | 66 (42.6) | 0.6354 |
| Delay between SSc onset and ILD onset, mean±SD | 4.0±7.0 | 3.5±7.5 | 4.0±7.0 | 0.5080 |
| Extent of lung parenchyma involved (%), median (IQR) | 30.0 (18.0-46.0) | 40.0 (26.0-47.0) | 28.5 (18.0-46.0) | 0.1322 |
| Extensive lung fibrosis, n(%) | 62 (29.5) | 20 (36.4) | 42 (27.1) | |
| Limited lung fibrosis, n(%) | 30 (14.3) | 6 (10.9) | 24 (15.5) | |
| Pulmonary patterns: | | | | |
| Ground-glass pattern, n(%) | 84 (91.3) | 24 (92.3) | 60 (90.9) | 1 |
| Honeycombing pattern, n(%) | 52 (56.5) | 17 (65.4) | 35 (53.0) | 0.3528 |
| Pleural reticularis, n(%) | 90 (97.8) | 25 (96.2) | 65 (98.5) | 0.4875 |
| Bronchiectasis, n(%) | 73 (79.3) | 21 (80.8) | 52 (78.8) | 1 |

Legend: interstitial lung disease (ILD); standard deviation (SD); years (y).

Exposed males most commonly worked in building (42.9%), foundry and metal factories (35.7%), and chemistry or cleaning works (16.7%, **Table 3**). Exposed females most commonly worked in foundry and metal factories, chemistry or cleaning works (27.0%), and in tissue fabric or dyeing professions (13.5 *vs*. 0% in males, p=0.01). No female worked in the building trade (p<0.0001). Exposure to crystalline silica was observed mostly in the building trade, foundry, and pottery or porcelain factories. Building, foundry and metal factories, chemistry industry and cleaning exposed to chlorinated or aromatic solvents, white spirit/hydrocarbons, formaldehydes and epoxy resins.

There was an association between occupational exposure and some aspects of disease severity. The CES was higher in patients with diffuse SSc (mean±SD 13.7±24.3 *vs*. 5.1±14.3 in patients with limited SSc, p<0.001). There was a trend of higher CES in patients with muscle weakness (9.2±15.4 *vs.* 8.0±19.3 in patients without muscle weakness, p=0.08). By contrast, the CES was similar in patients who developed ILD (10.0±22.8) and in patients who did not (6.4±15.3, p>0.05), both in the overall population and when analysis was restricted to males or females (not shown). No difference in CES was highlighted with regard to left heart disease, digestive tract involvement, or kidney injury (all p>0.05).

**Table 3.** Type of work of exposed patients

| | **All exposed N=79** | **Male N=42** | **Female N=37** | **P-value** |
|---|---|---|---|---|
| **Type of work** | | | | |
| Foundry and metals factories | 25 (31.6) | 15 (35.7) | 10 (27.0) | 0.8342 |
| Building Trade | 18 (22.8) | 18 (42.9) | 0 | **<0.0001** |
| Chemistry industry or cleaning works | 17 (21.5) | 7 (16.7) | 10 (27.0) | 0.1006 |
| Pottery or porcelain factories | 5 (6.3) | 1 (2.4) | 4 (10.8) | 0.1532 |
| Tissue fabric or dyeing work | 5 (6.3) | 0 | 5 (13.5) | **0.0101** |
| Farming | 1 (1.3) | 1 (2.4) | 0 | 1 |
| Welder | 1 (1.3) | 0 | 1 (2.7) | 0.4166 |
| Others | 7 (8.9) | 0 | 7 (18.9) | - |

Legend: data are described by total (%)

### 3.3. Variation in FVC and DLCOc over time: impact of occupational exposure and gender

We reviewed 1580 PFTs. A total of 144 patients had ≥4 PFTs and follow-up time >1 year. Mean duration of lung function follow-up was 11.1±6.8 years. Among these 144 patients, the median number of PFTs was 8 (range 4-30), mean FVC variation over time was -35.5±75.8 mL/year (-0.46±2.56 %predicted/year), and mean DLCOc variation was -240±769.8 mL/min/mmHg/year (-0.46±3.92 %predicted/year).

First, associations between yearly variation in lung function and known or suspected markers of accelerated decline were assessed. By univariate linear regression, both cumulative occupational exposure score and male gender were associated with yearly variation in FVC and DLCOc (all p<0.05, **Table 4**). Smoking, clinical form of SSc, history of digital ulcer or presence of PAH (for DLCOc), ILD involvement, positivity of anti-Scl70 antibodies or follow-up time were not associated with yearly variation in FVC or DLCOc (all p>0.05). By multivariate analysis, after adjustment for gender, the CES remained independently associated with yearly variation in absolute FVC value (p=0.003) and %pFVC (p=0.02, **Tables 4 & 5**).

**Table 4.** Changes in pulmonary functional parameters

| | **Univariate analysis** | | | **Multivariate analysis** | | |
|---|---|---|---|---|---|---|
| **Variables** | mean change of FVC [mL/year] | Std. Error | P.value | mean change of FVC [mL/year] | Std. Error | P.value |
| **Male gender** | -44.18 | 14.02 | **0.0019** | -19.73 | 16.00 | 0.2182 |
| **CES** | -1.20 | 0.29 | **<0.0001** | -0.99 | 0.33 | **0.0035** |
| **Tobacco smoking** | 2.56 | 13.19 | 0.8460 | - | - | - |
| **Diffuse cutaneous SSc** | -9.16 | 13.02 | 0.4829 | - | - | - |
| **SSc-ILD** | -11.06 | 12.65 | 0.3830 | - | - | - |
| **Topo I Ab positivity** | -2.30 | 13.67 | 0.8670 | - | - | - |
| **Follow-up time** | 0.21 | 0.81 | 0.7917 | - | - | - |

| | mean change of DLCOc [mL.min$^{-1}$.mmHg$^{-1}$.year$^{-1}$] | Std. Error | P.value | mean change of DLCOc [mL.min$^{-1}$.mmHg$^{-1}$.year$^{-1}$] | Std. Error | P.value |
|---|---|---|---|---|---|---|
| **Male gender** | -455.95 | 142.26 | **0.0016** | -329.40 | 169.93 | 0.0545 |
| **CES** | -7.29 | 3.02 | **0.0170** | -3.49 | 3.48 | 0.3163 |
| **Tobacco smoking** | 1.19 | 134.01 | 0.9929 | - | - | - |
| **Diffuse cutaneous SSc** | 1.21 | 132.48 | 0.9926 | - | - | - |
| **Presence of digital ulcer** | -234.67 | 127.85 | 0.0685 | -164.20 | 127.90 | 0.2013 |
| **PAH involvement** | 103.20 | 194.45 | 0.5964 | - | - | - |
| **SSc-ILD** | -20.70 | 128.84 | 0.8726 | - | - | - |
| **Topo I Ab positivity** | 80.86 | 138.71 | 0.5608 | - | - | - |
| **Follow-up time** | -3.89 | 8.31 | 0.6400 | - | - | - |

Legend: Cumulative exposure score (CES). Annual changes of forced vital capacity (FVC) and the hemoglobin-corrected transfer coefficient for carbon monoxide in the lung (DLCOc). Presence of interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), anti-Topoisomerase I/Scl70 antibodies (Topo I Ab).

Each one-point increase in cumulative occupational exposure score was associated with a mean variation in FVC of -0.99±0.33 mL/year ($R^2$= -.33, p<0.0001) after adjustment for gender (**Figure 2**).

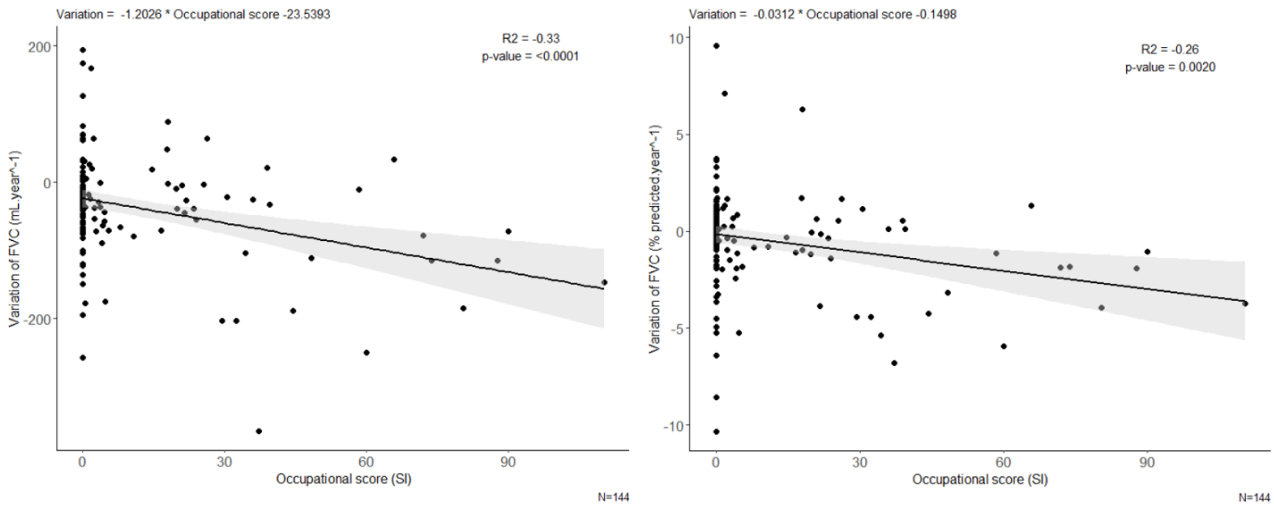


**Figure 2.** Regression slope between changes in FVC and cumulative exposure score

Legend: absolute value on left, and %predicted on right. standard index (SI); R squared coefficient by Pearson test.

By contrast, no predictor was independently associated with yearly variation in DLCOc (p=0.055, **Table 4**). Interestingly, FVC decline was similar in patients with (mean±SD -41.3±87.6) and without a diagnosis of ILD (-30.2±63.2 mL/year, p=0.12). The decline in DLCOc was also equivalent according to ILD status (p=0.48).

**Table 5.** Changes in pulmonary functional parameters expressed by percentage predicted

| | **Univariate analysis** | | | **Multivariate analysis** | | |
|---|---|---|---|---|---|---|
| **Variables** | mean change of FVC [%p/year] | Std. Error | P.value | mean change of FVC [%p/year] | Std. Error | P.value |
| **Male gender** | -0.73 | 0.43 | 0.0939 | -0.24 | 0.60 | 0.6799 |
| **CES** | -0.03 | 0.01 | **0.0020** | -0.03 | 0.01 | **0.0195** |
| **Tobacco smoking** | -0.01 | 0.44 | 0.9777 | - | - | - |
| **Diffuse cutaneous SSc** | -0.08 | 0.44 | 0.8576 | - | - | - |
| **SSc-ILD** | -0.06 | 0.42 | 0.8791 | - | - | - |
| **Topo I Ab positivity** | -0.22 | 0.46 | 0.6362 | - | - | - |
| **Follow-up time** | 0.05 | 0.02 | 0.0701 | -0.04 | 0.03 | 0.1478 |

| | mean change of DLCOc [%p/year] | Std. Error | P.value | mean change of DLCOc [%p/year] | Std. Error | P.value |
|---|---|---|---|---|---|---|
| **Male gender** | -1.22 | 0.74 | 0.1023 | -1.17 | 0.90 | 0.1963 |
| **CES** | -0.02 | 0.01 | 0.1524 | -0.01 | 0.02 | 0.5116 |
| **Tobacco smoking** | 0.06 | 0.68 | 0.9208 | - | - | - |
| **Diffuse cutaneous SSc** | 0.46 | 0.67 | 0.4904 | - | - | - |
| **Presence of digital ulcer** | -1.17 | 0.65 | 0.0745 | -0.82 | 0.66 | 0.2162 |
| **PAH involvement** | 0.58 | 0.99 | 0.5604 | - | - | - |
| **SSc-ILD** | -0.29 | 0.65 | 0.6533 | - | - | - |
| **Topo I Ab positivity** | 0.80 | 0.70 | 0.2529 | - | - | - |
| **Follow-up time** | -0.08 | 0.04 | **0.0459** | -0.10 | 0.04 | **0.0211** |

Legend: Cumulative exposure score (CES). Annual changes of forced vital capacity (FVC) and the hemoglobin-corrected transfer coefficient for carbon monoxide in the lung (DLCOc). Presence of interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), anti-Topoisomerase I/Scl70 antibodies (Topo I Ab).

When linear regression was restricted to males, both the cumulative occupational exposure score and a history of smoking remained independently associated with yearly variation in FVC (p=0.03 and 0.01 respectively, **Table 6 & Figure 3**).

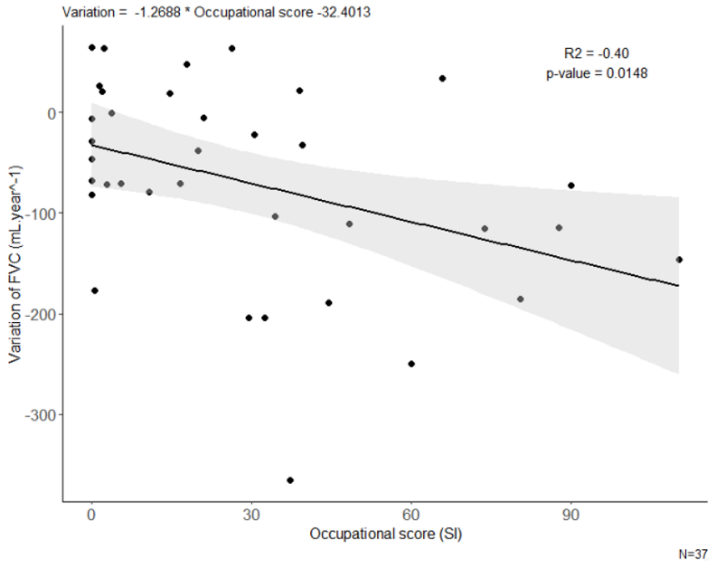


**Figure 3.** Regression slope between changes in FVC and CES in men

Legend: Forced vital capacity (FVC). Occupational score corresponded to cumulative exposure score (CES). Standard index (SI).

**Table 6.** Changes in pulmonary functional parameters restricted to men

| | **Univariate analysis** | | | **Multivariate analysis** | | |
|---|---|---|---|---|---|---|
| **Variables** | mean change of FVC [mL/year] | Std. Error | P.value | mean change of FVC [mL/year] | Std. Error | P.value |
| **CES** | -1.26 | 0.49 | **0.0148** | -1.02 | 0.46 | **0.0347** |
| **Tobacco smoking** | 91.88 | 30.98 | **0.0054** | 78.88 | 30.00 | **0.0127** |
| **Diffuse cutaneous SSc** | -7.30 | 33.43 | 0.8282 | - | - | - |
| **ILD involvement** | 31.14 | 32.325 | 0.3419 | - | - | - |
| **Topo I Ab positivity** | 20.47 | 32.56 | 0.5336 | - | - | - |
| **Follow-up time** | 2.02 | 2.19 | 0.3616 | - | - | - |

Legend: Presence of anti-Topoisomerase I/Scl70 antibodies (Topo I Ab), interstitial lung disease (ILD).

Univariate, but not multivariate, regression found a correlation between the CES and yearly variation in DLCOc in males (absolute value, $R^2$=-.20, p=0.01, **Figure 4**). In females, no association between the CES and yearly variation in lung function was found (data not shown). When we restricted the population to specific toxicant exposure, we also identified an inverse correlation between yearly variation in FVC and exposure to chlorinated solvents (absolute values only), crystalline silica, and epoxy resins (absolute values and %predicted, p<0.05 for all, **Figure 5**).

An inverse correlation was also found between the number of exposures and yearly variation in FVC ($R^2$=-.19, p=0.01, data not illustrated). The cumulative duration of exposure was also associated with yearly variation in FVC (p=0.03).

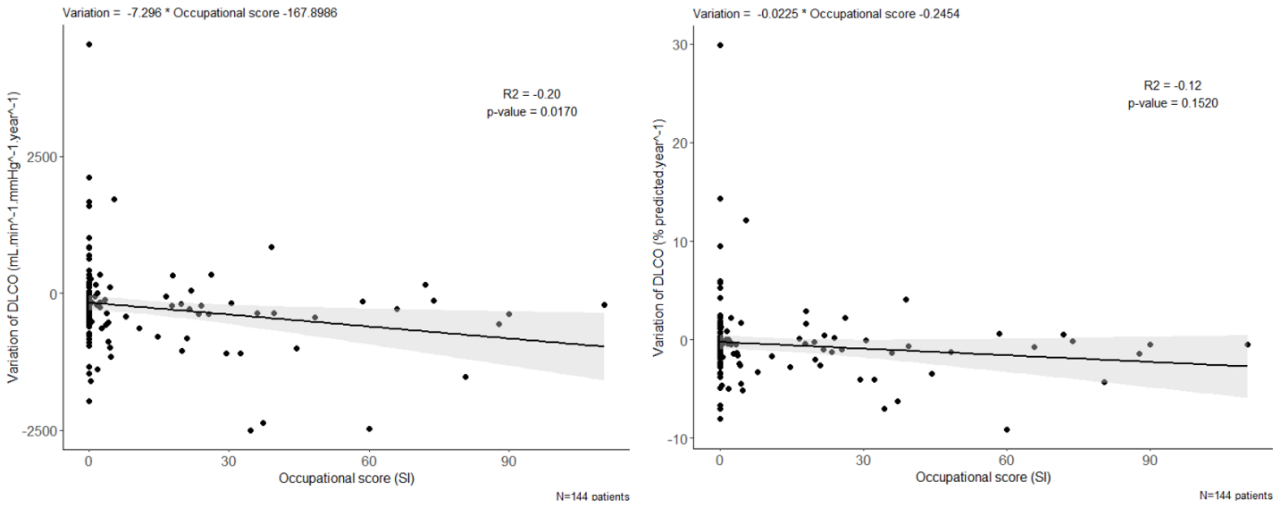


**Figure 4.** Regression slopes between changes in DLCOc and CES

Legend: absolute value on left, and %predicted on right. Hemoglobin-corrected transfer coefficient for carbon monoxide in the lung (DLCOc). Occupational score corresponded to cumulative exposure score (CES). Standard index (SI).

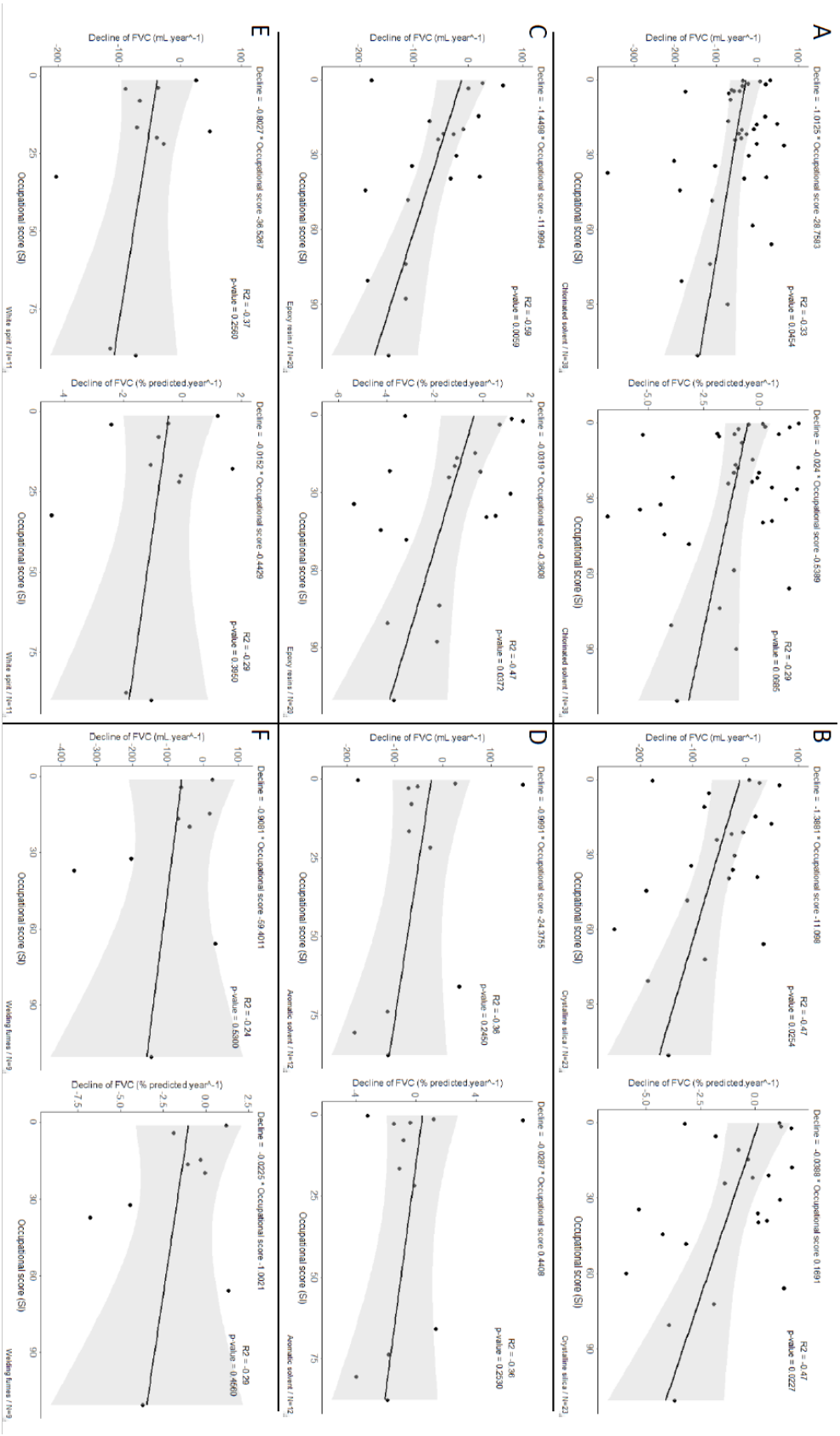


**Figure 5.** Regression slopes between changes in FVC and occupational exposure score restricted by toxic agent

Legend: restricted by exposure to chlorinated solvents (**A**; n=38), to crystalline silica (**B**; n=23), to epoxy resins (**C**; n=20), to aromatic solvents (**D**; n=12), to white spirit (**E**; n=11), to welding fumes (**F**; n=9). Occupational score corresponded to cumulative exposure score (CES). Forced vital capacity (FVC).

Second, we assessed the potential predictor factors associated with decline ≥10% in FVC or ≥15% in DLCOc at any time from baseline, using univariate and multivariate regression models. Over the follow-up period, 54/144 (37.5%) patients reached a decline ≥10% in FVC at any time and 38/144 (26.4%) reached a decline ≥15% in DLCOc at any time from baseline. The CES was independently associated with occurrence of decline ≥10% in FVC at any time from baseline (p=0.01, **Table 7**). No impact of gender, tobacco smoking, cutaneous SSc form, positivity of anti-Scl70 antibodies or follow-up time was identified. No predictor factor was found concerning decline ≥15% in DLCOc.

Finally, we explored the impact of gender and occupational exposure on time to decline ≥10% in FVC or ≥15% in DLCOc. Males tended to have a shorter time to decline in FVC than females (mean ±SD 6.0±6.1 *vs*. 8.3±6.2 years, p=0.054). A trend was also found concerning exposure status (6.7±6.1 in exposed patients *vs*. 8.4±7.2 years, p=0.078). Neither gender nor occupational exposure status were associated with a shorter time to DLCOc decline. Time to decline ≥10% in FVC or ≥15% in DLCOc was assessed by a Cox model with calculation of Hazard Ratios (HR), with adjustment for gender, cumulative exposure score, and follow-up time. Through this analysis, neither the CES (HR =1.01 [95%CI 0.99-1.02]) nor male gender (HR =1.33 [95%CI 0.76-2.36]) were independently associated with a shorter time to decline in lung function. The event curve is illustrated in **Figure 6**, with exposure as a categorical variable. There was no difference in time to decline of DLCOc ≥15% in relation to male gender (HR =1.07 [0.60-1.90]), and after adjustment either for CES (HR =1.00 [0.98-1.01]) or follow-up time (HR =0.96 [0.93-0.99], p=0.03).

**Table 7.** Predictive factors associated with a decline ≥10% of FVC

| Decline FVC≥10% | Label | No Decline n(%) | Decline n(%) | OR(95%CI) (univariate) | OR(95%CI) (adjusted - complete) | OR(95%CI) (adjusted - final) |
|---|---|---|---|---|---|---|
| **Gender** | Female | 67 (76.1) | 38 (70.4) | - | - | - |
| | Male | 21 (23.9) | 16 (29.6) | 1.34 (0.62-2.88, p=0.448) | 0.53 (0.17-1.55, p=0.259) | - |
| **CES (SI)** | Mean (SD) | 5.8 (13.6) | 17.2 (28.2) | **2.80 (2.75-2.86, p=0.005)** | **2.80 (2.75-2.89, p=0.006)** | **2.80 (2.75-2.86, p=0.011)** |
| **Tobacco smoking** | No smoking | 56 (63.6) | 35 (64.8) | - | - | - |
| | Smoking | 32 (36.4) | 19 (35.2) | 0.95 (0.46-1.92, p=0.887) | 0.87 (0.38-1.99, p=0.749) | - |
| **SSc form** | Limited | 60 (68.2) | 28 (51.9) | - | - | - |
| | Diffuse | 28 (31.8) | 26 (48.1) | 1.99 (0.99-4.02, p=0.053) | 1.69 (0.66-4.40, p=0.273) | 1.58 (0.76-3.30, p=0.221) |
| **SSc-ILD** | Without | 48 (54.5) | 26 (48.1) | - | - | - |
| | Presence of ILD | 40 (45.5) | 28 (51.9) | 1.29 (0.66-2.56, p=0.459) | 0.79 (0.33-1.86, p=0.600) | - |
| **Topo I Ab positivity** | Negative | 64 (72.7) | 34 (63.0) | - | - | - |
| | Positive | 24 (27.3) | 20 (37.0) | 1.57 (0.76-3.24, p=0.223) | 1.33 (0.50-3.55, p=0.565) | - |
| **Follow-up time (years)** | Mean (SD) | 14.2 (7.6) | 14.0 (8.1) | 1.00 (0.95-1.04, p=0.910) | 1.00 (0.96-1.05, p=0.853) | - |

Legend: Cumulative exposure score (CES). Interstitial lung disease (ILD). Anti-Topoisomerase I/Scl70 antibodies (Topo I Ab). Odds ratio (OR), 95% confidence interval (95%CI). Standard Index (SI).

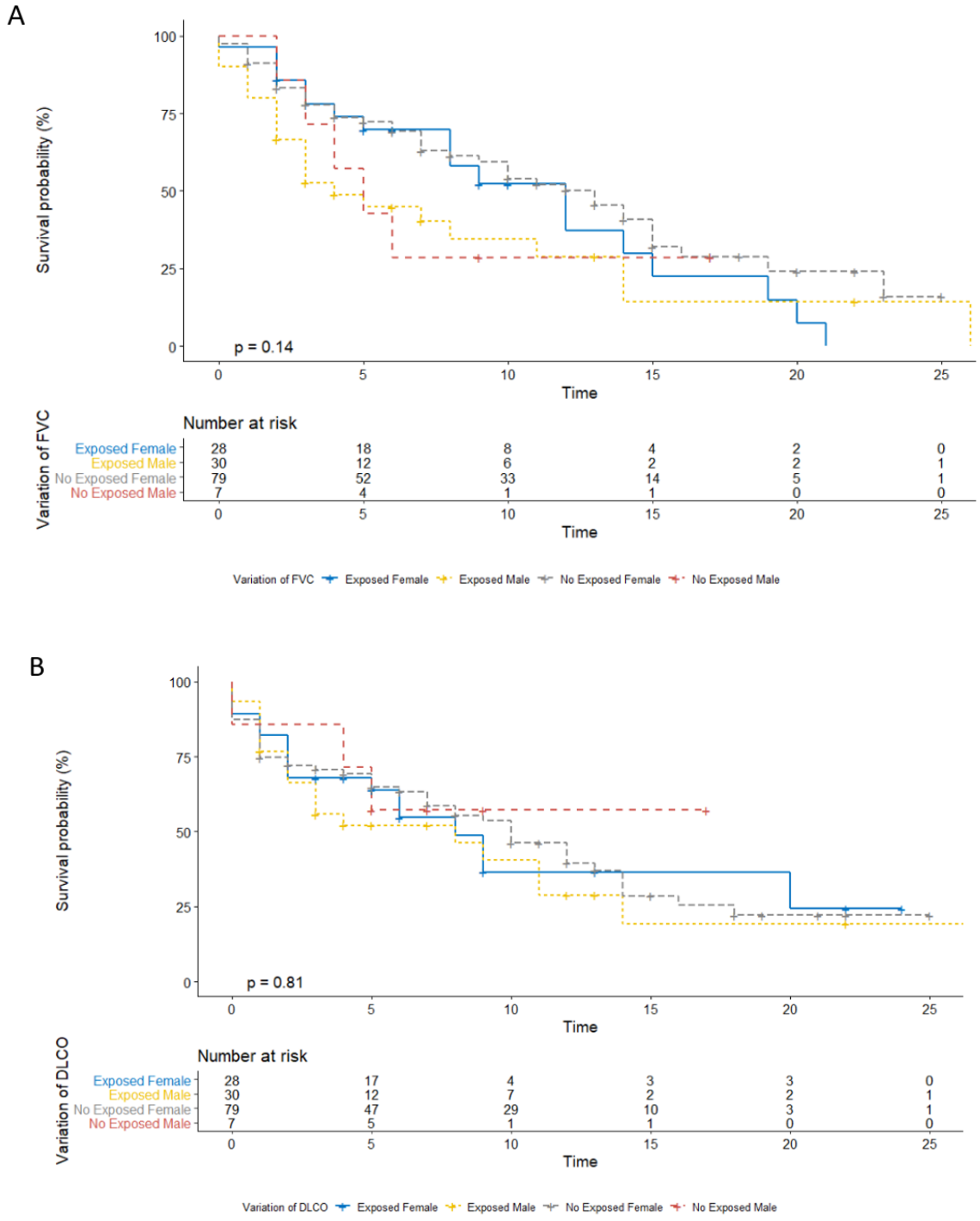


**Figure 6.** Time to decline of FVC and DLCOc interpreted as categorical variables during follow-up

Legend: Progression-free survival of FVC on top (Panel **A**) and DLCOc at the bottom (Panel **B**) according to combined gender and exposure status. Hemoglobin-corrected transfer coefficient for carbon monoxide in the lung (DLCOc). Forced vital capacity (FVC).

## 4. Discussion

In this study, we retrospectively analyzed a large cohort of SSc patients followed over 10 years. This study is the first to demonstrate that occupational exposure is independently and dose-dependently associated with decline in FVC over time. By contrast, male gender was not an independent predictor factor of lung function decline. This study highlighted the high prevalence of occupational exposure in male patients with SSc and its impact on the course of SSc.

**This study highlighted the high prevalence of occupational exposure in patients with SSc, especially in males.** Occupational exposure was strongly over-represented in males, especially for crystalline silica and organic solvents, similar to others studies (11,12,14,31). The frequency of occupational exposure in SSc patients varies greatly from study to study, possibly due to recall bias in retrospective studies, or to variations in methods of exposure assessment. We found that 24% of females were exposed to at least one toxicant. As reported by others (32,33), gender differences in exposure were related to differences in occupation history, most notably in the fields of building (males) and tissue or dyeing works (females).

**Taking advantage of a large cohort of SSc patients with long follow-up and systematic, quantitative assessment of occupational exposure, this study was the first to demonstrate a gender-independent correlation between occupational exposure and FVC decline over time in SSc**. A dose-effect relationship was demonstrated since for each supplemental point of cumulative exposure score (CES), FVC declined with a mean of 1 mL/point/year. Correlations with yearly decline in FVC were strongest for exposure to chlorinated solvents, crystalline silica or epoxy resin, and there was an association with the number of toxicants. In contrast to other reports, we did not observe any association between lung function decline and either digital ulcers, PAH (17), diffuse cutaneous sclerosis (8) or anti-Scl70 antibodies (29). Strikingly, SSc-ILD was not associated with a decline in either FVC or DLCOc in this cohort, at variance with previous reports (34). Smoking status could be evoked as a cofounding factor in our results, since it was more frequent in males

(31). No association was found, however, between tobacco history and lung function decline in the total population, and the model was adjusted for tobacco smoking in males (Tables 4 & 5).

**Yearly decline in both FVC and DLCOc was consistent with those reported by previous authors**. Decline in FVC and DLCOc was similar to Le Gouellec et *al*., who reported that FVC declined by 0.1±0.3%/year, and DLCO by 1.5±0.3%/year (17) in patients with SSc. These values were lower than those reported by Khanna *et al.* in the placebo arm of the Scleroderma Lung Study trial, where patients were selected for SSc-ILD with active alveolitis (34).

In addition to the yearly decline in FVC, the cumulative occupational exposure score was independently associated with the occurrence of FVC decline ≥10% from baseline. Interestingly, although there was a gender-independent correlation between occupational exposure and FVC decline over time, neither **gender nor occupational exposure was independently associated with time to a predefined decrease in lung function**. This discrepancy may be explained by gender- and age-specific differences in lung function trajectories. For instance, while FVC is higher in adult males in comparison to females, FVC decline over time is quicker in males in the 25-60 year range, as reported by the Global Lung Initiative task force (35). Thus, analyses of lung function decline based on predefined thresholds may skew results towards increased weight of gender and age, at the expense of other factors. Thus, whether gender impacts lung function decline over time in SSc remains controversial (16,17), although male gender is reportedly associated with faster progression of ILD on HRCT (36).

**In this study, the prevalence of ILD in males was close to 50%, similar to women**. This result was in line with some previous studies (37–40), although other authors have reported a higher prevalence of SSc-ILD in males (12,31,41). In contrast with less recent studies, SSc-ILD diagnoses in our study were based on HRCT data. **Current data predominantly, although not unequivocally** (13,42)**, suggest that occupational exposure may not be an independent risk**

**factor for SSc-ILD, consistent with our observations.** Likewise, in two recent Brazilian and Australian cohorts, patients with exposure to environmental factors or silica had a similar prevalence of SSc-ILD compared to patients without exposure (14,43). In a recent prospective study conducted in patients with early SSc, male gender was not associated with a greater prevalence of SSc-ILD, HRCT abnormalities, or progression of SSc-ILD (44).

An intriguing observation was the discrepancy between, on the one hand, a significant association between occupational exposure and decline in lung volumes (FVC), and on the other hand, the lack of an association between occupational exposure and a diagnosis of SSc-ILD. Decrease in lung volumes can result from reduction in lung compliance, reduction in chest wall compliance, or reduction in respiratory muscle strength. Since occupational exposure was not associated with a decline in DLCOc, a sensitive marker of lung damage, one may hypothesize that lung-independent mechanisms may explain the impact of occupational exposure on FVC in patients with SSc. In support of this hypothesis, extensive skin fibrosis and progression of skin fibrosis defined as an increase in mRSS >5 and ≥25% from baseline to 12±3 months, was independently associated with FVC decline ≥10% (8). In recent findings by Nawata et *al*., chest wall muscle atrophy correlated with decline in FVC, but not with the extent of ILD, while variations in muscle involvement and ILD extent are independently associated with FVC decline (9). Another study involving 1145 Canadian SSc patients confirmed the impact of muscle involvement on the decrease in FVC (45). Prevalence of sarcopenia may reach 25% in SSc, with a high impact on functional disability independently of SSc-ILD (46). Aguila et *al*. recently reported a higher prevalence of myopathy in SSc patients with environmental exposure (14).

**Many aspects of SSc pathogenesis remain unclear, especially with regard to implication of gender and exposure.** Due to the strong female preponderance in SSc, a role of female hormones in disease susceptibility is suspected. Sex hormones can affect the immune system and quantitatively

modulate immune responses. The effect of toxic agents in the pathophysiology of SSc is not yet fully understood. *In vitro* and *in vivo* data have shown that silica induces ectopic lymphoid neogenesis, selection of autoreactive T-cell populations, and production of profibrotic and proinflammatory factors by macrophages (47). Silica may induce autoimmunity and alteration of Fas-mediated apoptosis, especially in regulatory T-cells (48). Solvents, which may penetrate the body by the transcutaneous and inhaled routes, may induce humoral and cellular autoimmune responses, along with the production of profibrotic factors and vascular remodeling (49,50).

**Our study has strengths and limitations.** The key strength of the present study was the use of a method for precise quantitation of occupational exposure (26–28), which allowed us to analyze the effect of exposure independently of the effect of gender, under the hypothesis that intensity of exposure had an impact on lung function decline. Of note, systematic assessment of exposure led to a higher proportion of exposed women in comparison with others studies. Although other authors have assessed the impact of occupational exposure as a risk factor for SSc-ILD, none have evaluated its impact on lung function decline (26,27,32,33). The retrospective design led to heterogeneity in delays between PFTs and follow-up time. This bias was limited by selecting patients with more than 4 PFTs to average lung function trajectories among patients. Also, the retrospective design precluded exploration of muscle weakness and skin changes over time, and thus of the relationships between occupational exposure and either skin or muscle disease. The choice of ECCS93 lung function reference values over most recent values was justified by the fact that most data were historical. A higher number of subjects might have increased the number of unexposed men to better tease apart the independent impacts of gender and exposure.

# 5. Conclusion

In conclusion, we show that intensity of occupational exposure is independently associated with accelerated FVC decline in patients with SSc in a dose-response relationship. This study confirms the high prevalence of occupational exposure in SSc patients, with over-representation in males. Quantitative assessment of occupational exposure may provide a valuable tool for SSc prognostication. Avoidance of occupational exposure to toxicants should be a high priority in patients with SSc.

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# 7. Annex

## 7.1. Annex 1. ACR/EULAR 2013 Criteria

| Domaine | Critères * | Score # |
|---|---|---|
| Épaississement cutané (ne tenir compte que du score le plus élevé) | Épaississement cutané des doigts des mains s'étendant au-delà des articulations MCP | 9 |
| | Doigts boudinés | 2 |
| | Atteinte des doigts ne dépassant pas les articulations MCP | 4 |
| Lésions pulpaires (ne tenir compte que du score le plus élevé) | Ulcères pulpaires digitaux | 2 |
| | Cicatrices déprimées | 3 |
| Télangiectasies | | 2 |
| Anomalies capillaroscopiques | | 2 |
| Atteinte pulmonaire | HTAP et/ou fibrose pulmonaire | 2 |
| Phénomène de Raynaud | | 3 |
| Anticorps spécifiques de la ScS | Anti-topoisomérase I<br>Anticorps anti-centromères<br>Anti-ARN polymerase de type III | 3 |

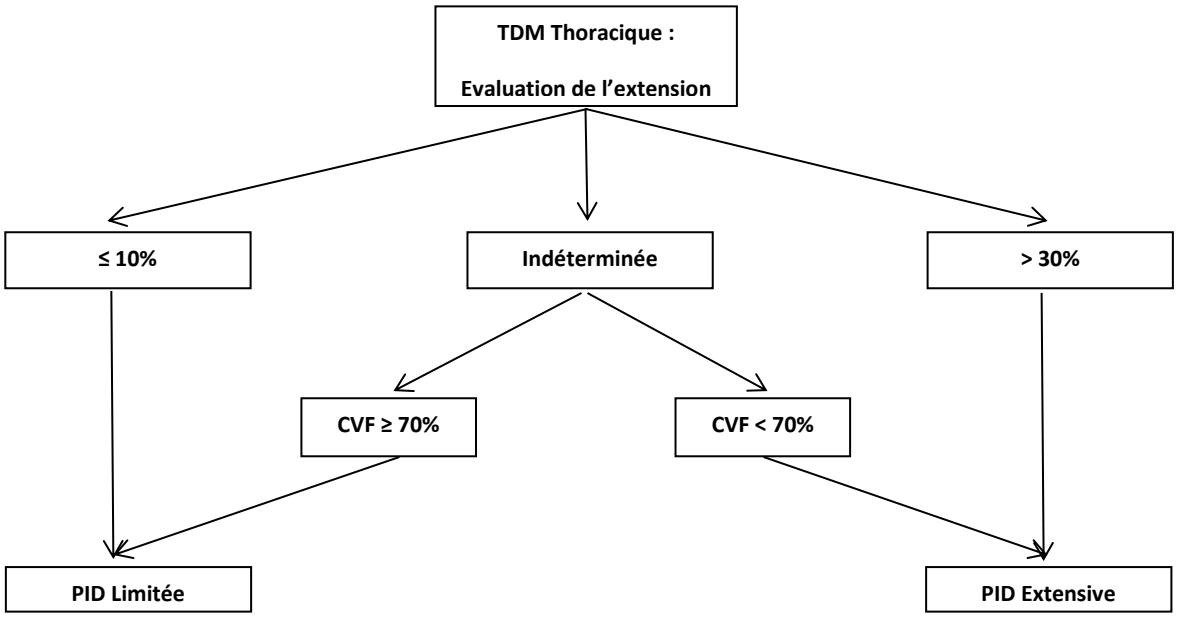
## 7.2. Annex 2. SSc-related interstitial lung disease assessment

Nom :..... DDN :..... Date TDM : ...../...../.....

Prénom :..... IPP :.....

CVF :..... date EFR : ...../...../..... (si nécessaire)

Evaluation de la PID associée à la SSc




| | Pattern PID (%) | Verre dépoli (0/1) | Rayon de miel (0/1) | Réticulations ss pleurale (0/1) | Bronchectasie (0/1) |
|---|---|---|---|---|---|
| **Origine gros Vx** | | | | | |
| **Carène** | | | | | |
| **Confluence V.pulm** | | | | | |
| **Mi chemin 3ème /4ème niveaux** | | | | | |
| **Au dessus hemi-diaphragme Dt** | | | | | |
| **Somme des scores** | | | | | |
| **Moyenne des sommes** | | | | | |

- **Cotation :** évaluation **à 5% près** de l'extension par niveau d'analyse
- **Score total :** moyenne des scores par niveaux

## 7.3. Annex 3. Occupational exposure assessment questionnaire

Nom : ……. Prénom : ……. N° Anonymat :…….

Date de naissance : ……./……./…….

Adresse complète : ……..

Téléphone : ……

>----------

Sexe : ☐ Masculin ☐ Féminin

Dans les 5 ans avant le début de la maladie :

- Avez-vous vécu à moins de 5 km d'un aéroport international ? ☐Oui ☐Non
- Avez-vous vécu à moins de 5 km d'une mine ou carrière de roche ? ☐Oui ☐Non
- Vivez-vous dans une ville de plus de 200 000 habitants ? ☐Oui ☐Non

Antécédents médicaux, chirurgicaux, gynéco-obstétricaux : (dates des grossesses)

Antécédents d'infection virale (VHB, VHC, VIH, HTLV-1, EBV, Cocsakie, HTLV-1 …) :

Antécédents familiaux de maladie auto-immune ou de syndrome de Sjögren :

Maladie et traitements actuels (autres que le syndrome de Sjögren) :

Contraception : ……. Traitement hormonal substitutif de la ménopause : ……

Tabac : Fumeur : ☐ Non ☐ Oui ; Paquets-années : ……..

Ancien fumeur : ☐ Non ☐ Oui ; Paquets-années : ……..

Date d'arrêt : ……..

N° Anonymat :…….

Port de lentille de contact : ☐Oui ☐Non

Port de prothèse mammaire : ☐Oui ☐Non

Port de prothèse testiculaire ☐Oui ☐Non Autre prothèse : ……

Pratique de teintures capillaires, permanentes, coloration ou décolorations :

☐ Jamais

☐ Moins d'une fois par trimestre

☐ Au moins une fois par trimestre

☐ Au moins une fois par mois

☐ Au moins une fois par semaine

Utilisation de cabine U.V. (ultra-violet) :

☐ Jamais

☐ Moins d'une fois par trimestre

☐ Au moins une fois par trimestre

☐ Au moins une fois par mois

☐ Au moins une fois par semaine

Catégorie socio-professionnelle :

☐ Agriculteur exploitant

☐ Employé de bureau

☐ Employé de commerce

☐ Ouvrier

☐ Cadre, agent de maîtrise, technicien

☐ Personnel de service ou autre (santé, éducation, action sociale…)

☐ Professions libérales

☐ Clergé, armée, police

N° Anonymat :…….

Indiquer ici l'intitulé de tous vos emplois et poste de travail (en étant le plus exhaustif possible) :

1/ Période du …… au …….

| | | | |
|---|---|---|---|
| Prévention technique au poste de travail : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Protection individuelle respiratoire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Par gants : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Oculaire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Buccale : | ☐ Non | ☐ Oui | ☐ Ne sait pas |

2/ Période du …… au …….

| | | | |
|---|---|---|---|
| Prévention technique au poste de travail : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Protection individuelle respiratoire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Par gants : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Oculaire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Buccale : | ☐ Non | ☐ Oui | ☐ Ne sait pas |

3/ Période du …… au …….

| | | | |
|---|---|---|---|
| Prévention technique au poste de travail : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Protection individuelle respiratoire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Par gants : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Oculaire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Buccale : | ☐ Non | ☐ Oui | ☐ Ne sait pas |

4/ Période du …… au …….

| | | | |
|---|---|---|---|
| Prévention technique au poste de travail : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Protection individuelle respiratoire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Par gants : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Oculaire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Buccale : | ☐ Non | ☐ Oui | ☐ Ne sait pas |

N° Anonymat :…….

5/ Période du ……. au …….

| | | | |
|---|---|---|---|
| Prévention technique au poste de travail : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Protection individuelle respiratoire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Par gants : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Oculaire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Buccale : | ☐ Non | ☐ Oui | ☐ Ne sait pas |

6/ Période du ……. au …….

| | | | |
|---|---|---|---|
| Prévention technique au poste de travail : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Protection individuelle respiratoire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Par gants : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Oculaire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Buccale : | ☐ Non | ☐ Oui | ☐ Ne sait pas |

7/ Période du ……. au …….

| | | | |
|---|---|---|---|
| Prévention technique au poste de travail : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Protection individuelle respiratoire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Par gants : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Oculaire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Buccale : | ☐ Non | ☐ Oui | ☐ Ne sait pas |

8/ Période du ……. au …….

| | | | |
|---|---|---|---|
| Prévention technique au poste de travail : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Protection individuelle respiratoire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Par gants : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Oculaire : | ☐ Non | ☐ Oui | ☐ Ne sait pas |
| Buccale : | ☐ Non | ☐ Oui | ☐ Ne sait pas |

Loisirs et environnement :

Utilisez-vous ou avez-vous utilisé régulièrement (au moins une fois par semaine) durant vos loisirs ?

Colles, vernis, peintures, encres : ☐ Non ☐ Oui ☐ Ne sait pas

Si oui, pendant combien d'année ? …….

---

Essence, diluants, dégraissant, solvants : ☐ Non ☐ Oui ☐ Ne sait pas

Exemple : white spirit ou essence de térébenthine

Si oui, pendant combien d'année ? …….

---

Pesticides (engrais, insecticides, désherbants …) : ☐ Non ☐ Oui ☐ Ne sait pas

Si oui, pendant combien d'année ? …….

---

Résines pour la fabrication de skis,

surfs, raquette, planche à voile, bateau : ☐ Non ☐ Oui ☐ Ne sait pas

Si oui, pendant combien d'année ? …….

---

Produits pour le développement des photographies : ☐ Non ☐ Oui ☐ Ne sait pas

Si oui, pendant combien d'année ? …….

---

Outils vibrants portés à la main : ☐ Non ☐ Oui ☐ Ne sait pas

Exemple : perceuse à percussion, meuleuses, scies à chaines, tronçonneuse, débroussailleuses …)

Si oui, pendant combien d'année ? …….

---

Applications de crème sur le visage : ☐ Non ☐ Oui ☐ Ne sait pas

Si oui, pendant combien d'année ? …….

Noms de produits utilisés : …….

---

Application cutanée autre que le visage : ☐ Non ☐ Oui ☐ Ne sait pas

Si oui, pendant combien d'année ? …….

---

Noms de produits utilisés : …….

---

Matériaux susceptibles de dégager des poussières : ☐ Non ☐ Oui ☐ Ne sait pas

---

Avez-vous été expos à l'un des produits suivants durant l'exercice de votre profession, et si oui pendant combien de temps : COCHER LA REPONSE EXACTE

| | OUI | NON | NE SAIT PAS | DUREE |
|---|---|---|---|---|
| Silice | | | | |
| Silicone | | | | |
| Trichloréthylène | | | | |
| Perchloréthylène<br>Tétrachloroéthylène | | | | |
| Trichloréthane<br>(baltane) | | | | |
| Benzène | | | | |
| Toluène | | | | |
| White Spirit | | | | |
| Naphta-N-hexane | | | | |
| Héxachlorétane | | | | |
| Chlorure de vinyle | | | | |
| Résine époxy | | | | |
| Pesticides | | | | |
| Fumée de soudure | | | | |
| Pousssière de :<br>Mortier<br>Craie<br>Céramique<br>Plâtre<br>Bois<br>Filtre de bois | | | | |
| Métaux | | | | |
| Autres : | | | | |

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**Résumé :**

**Objectif**: Le genre masculin et l'exposition occupationnelle (EO) aux substances toxiques sont des marqueurs de mauvais pronostic dans la Sclérodermie Systémique (ScS). L'objectif était d'évaluer l'impact respectif du genre et de l'EO sur les caractéristiques des patients atteints de ScS et sur la variation de la capacité vitale forcée (CVF) et de la capacité de diffusion du monoxyde de carbone corrigée par l'hémoglobine (DLCOc).

**Méthodes**: Les patients atteints de ScS avaient une évaluation quantitative de l'EO via un score cumulatif d'exposition (SCE). L'association entre le SCE et les caractéristiques était explorée chez 210 patients. L'association entre le SCE et la variation de la CVF et de la DLCOc était évaluée chez 144 patients avec ≥4 mesures de la fonction pulmonaire sur ≥1 an, via des modèles uni et multivariés.

**Résultats**: Le genre masculin était associé à l'EO (OR =10,3 [IC à 95% 5,1-21,9], p <0,0001). Le SCE était plus élevé chez les patients atteints de forme diffuse que limitée. Le SCE était indépendamment associé à la variation annuelle de la CVF au cours du temps, en particulier chez les hommes (p = 0,03), à une baisse de la CVF ≥10% par rapport à la base (p = 0,01), et inversement corrélé avec la variation annuelle de la CVF (R2 = -,33, p <0,0001). La prévalence de la pneumopathie interstitielle diffuse était similaire selon le genre ou le statut d'exposition.

**Conclusion**: L'EO est indépendamment associé au déclin de la CVF avec une relation dose-effet, mais pas au déclin de la DLCOc ou de la maladie pulmonaire interstitielle. L'évaluation de l'exposition correspond à un outil d'évaluation pronostique de la ScS. L'éviction de l'exposition professionnelle devrait être une priorité dans la ScS.



**Mots clés :** Sclérodermie Systémique, Genre, Exposition occupationnelle, Déclin de la CVF


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