Review

Systemic Sclerosis: Environmental Factors

GABRIELA FERNANDA MORA

ABSTRACT. Epidemiological evidence for the association between environmental and occupational risk factors and systemic sclerosis (SSc) has been extensively analyzed. Such exposures are frequently of long duration, and the inadequate classification of the type of exposure and other confounding variables may bias their estimated association with SSc. Environmental factors could be classified as occupational (silica, organic solvents), infectious (bacterial, viral), and non-occupational/non-infectious (drugs, pesticides, silicones). Understanding the link between environmental risk factors and the development of SSc is limited, due to the phenotypic and pathogenic heterogeneity of patients and disease, respectively, and also due to poor ability to assess environmental exposures quantitatively and the role of the gene-environment interactions in this disease. Global collaboration could increase the chance for a better use of the data obtained from a limited number of cases and also limited resources. Normalization and validation of biomarkers and questionnaires could also be very useful to reliably quantify environmental exposures. (First Release Oct 1 2009; J Rheumatol 2009; 36:2383–96; doi:10.3899/ jrheum.090207)

Key Indexing Terms:
SYSTEMIC SCLEROSIS
EPIDEMIOLOGY
RISK FACTORS
ENVIRONMENTAL EXPOSURE

Understanding the role of environment in autoimmune disease pathogenesis is limited even in the genomic era. Environmental risk factors are identified when autoimmunity emerges after certain exposure, resolves when that exposure has stopped and relapses at rechallenge.

Environmental disease risk factors can be identified by means of several standardized methods when there are uniform systematic criteria to be applied by the investigators. However, there is a limited number of validated exposure biomarkers and other tools for environmental assessment; physicians lack accurate knowledge in environmental medicine; systemic autoimmune diseases are rare; and there are no national databases on autoimmune diseases to enhance epidemiologic research, making it difficult to define environmental risk factors for autoimmunity. That is the reason why epidemiologic research with the accurate power to identify environmental risk factors in autoimmune diseases may require an important sample size, resulting in unpractical and expensive studies.

Environmental etiology of systemic sclerosis (SSc) has been extensively investigated. Clusters of disease have been identified among certain occupational groups[1-7], and small descriptive research has identified a variety of environmental agents such as vinyl chloride[8-10], silica[1-5,7,11-13], certain hydrocarbons[14,15], epoxy resins[16], rapeseed oil[17], drugs[18-22], and vaccines[23] (Table 1). There is a growing body of evidence related to the "spacio-temporal" cluster in systemic sclerosis etiology[24-27].

From Departamento de Docencia e Investigación — HMC Cir My Dr Cosme Argerich; and Facultad de Medicina, Universidad de Buenos Aires, UDH "J," Buenos Aires, Argentina.

G.F. Mora, MD, PhD.

Address correspondence to Dr. G.F. Mora, HMC Cir My Dr Cosme Argerich, Docencia e Investigación, Luis M. Campos 726, Buenos Aires, 1426 Argentina.

Accepted for publication May 12, 2009.

PATHOPHYSIOLOGY

Mechanisms responsible of the development of environmentally induced systemic autoimmunity are poorly understood. There are several hypotheses, but none of them are accurately sustained by direct evidence. Those mechanisms supposed to be involved in the beginning of the disease may be different to those worsening an established disease.

Environmental pathogenesis of SSc may be divided into 3 major mechanisms[28], as follows.

Immune Tolerance Interference

Loss of self-tolerance is crucial for the development of autoimmunity as a general concept. Many studies suggest that environmental exposure to certain agents affects tolerance at several points.

The haptene hypothesis proposes that a drug or its metabolites bind to certain proteins, changing their immunogenicity and triggering an immune response. The T cell recognition of such a complex is altered and results in immune tolerance interference. Human lymphocytes stimulated with silica express high levels of Fas receptor (CD95) and undergo apoptosis, with autoantigen alteration, concentration, and release, provoking an autoimmune attack[29] and post-translational protein changes[28].

Epigenetics comprise all inherited changes in gene expression that are not coded in the DNA sequence itself.

Table 1. Environmental factors associated with SSc.

1 Silica, silicon, and silicones	
Silica dust	Gold and coal miners
	Stone masons
	Abrasive powder work
Breast Implants	Silicone
	Paraffin
2 Inorganic compounds	
Aromatic hydrocarbons	Toluene
	Benzene
	Xylene
	Aromatic blends (diesel, etc.)
Aliphatic hydrocarbons	
Chlorated	Vinyl chloride
	Trichloroethylene
	Perchloroethylene
	Naphta-n-hexane
Non chlorated	
Epoxy resins	
Biogenic amines	
Urea-formaldehyde foam	
3 Drugs	Bleomycin
	Carbidopa
	L-5-hydroxytryptophan
	Pentazocine
	Cocaine
	Appetite suppressants
	Diethylpropion
	Fenfluramine chlorohydrate
4 Rapeseed oil	
5 L-tryptophan	

Two major mechanisms mediate epigenetic changes: DNA methylation and histone modification[30-33]. There is a direct causal relationship between methylation-dependent transcriptional repression and histone modifications. Some drugs may alter genomic activity by means of changes on DNA structure. Methylation of DNA suppresses genetic activity and regulates genes potentially harmful for cell functions. Hydralazyne and procainamyde are examples of DNA methylation inhibitors that enhance the expression of normally silenced genes and may lead to autoimmunity[33-37].

Scleroderma-associated cellular abnormalities persist in multiple generations of SSc fibroblasts *in vitro* and this profibrotic phenotype persists outside the disease microenvironment, suggesting the inheritance and transmission of *in vivo* imprinting of this disease phenotype among generations of fibroblasts. Increased levels of epigenetic mediators in SSc fibroblasts were noted in a study by Wang and colleagues[30]. The augmented collagen synthesis by SSc fibroblasts was linked to epigenetic repression of the collagen suppressor gene *FLI1*. Heavy methylation of the CpG islands in the *FLI1* promoter region was demonstrated in SSc fibroblasts and skin biopsy specimens.

Immune System Activation

It has been postulated that many cases of autoimmunity that occur after the therapeutic administration of cytokines and resolve after withdrawal may be the result of the direct immune activation by these cytokines. Other studies show that respirable silica particles are phagocytized by alveolar macrophages, driving cell activation and release of soluble mediators such as cytokines: tumor necrosis factor-α, interleukin 1-ß, and transforming growth factor-ß[38]. T cell incubation with silica and silicates may cause lymphoid polyclonal activation *in vitro*[29].

The role of solvents in the initiation of SSc is not clear. Autoimmune disease-prone MRL +/+ mice exposed to trichloroethylene (TCE) and its metabolites induced autoantibody production[39]. In a population exposed to domestic contamination of water with TCE, there were found high levels of CD4+ CD8+ T lymphocytes in peripheral blood, suggesting that this agent may alter normal immunity by modification of autoantigens[40]. Solvents penetrate through the skin and the airways, initiating cellular and humoral autoimmunity and stimulating the production of fibrogenic proteins and growth factors[41].

Vinyl chloride can enhance the immunogenicity of certain intracellular molecules, CD8+ activation[42], and skin thickening related to collagen deposition[43].

Molecular Mimicry

This mechanism is characterized by an immune response to an environmental agent cross-reacting with the host antigens. The best epidemiologic evidence for this mechanism in human disease is beta-hemolytic streptococci infection and rheumatic fever[44]. It is challenging to elucidate if this cross-reactivity is an epiphenomenon of such infection, or if autoimmunity appears after a loss of T cell ability to discriminate self- from non-self antigens through the shared epitope mechanism[45].

Maul, *et al* identified an 11-amino acid epitope on the C-terminal extreme of topoisomerase (topo)-1 sharing 6 of 11 sequential amino acids of the group-specific antigen p30gag from certain mammal retroviruses[46]. Muryoi and colleagues described an epitope the recognizes the N-terminal extreme of topo-1 in patients with SSc and TSK mice. This epitope seems to have a cross-reactivity with other fragments of topo-1 and shares some degree of homology with UL70 protein of human cytomegalovirus (HCMV)[47].

There may be no single mechanism to explain environmental exposure triggering such an heterogeneous disease as SSc. It is more likely to exist a combination of all these mechanisms. Most of the alterations of the immune system may involve antigen recognition and processing, cell signaling, and cytokine production.

New approaches in biology have led to the implementation and combination of genomic, proteomic, and metabolomic studies, bringing us closer to identifying the molecular signature of some environmental exposures.

EPIDEMIOLOGY

Epidemiologic evidence for the association between environmental and occupational risk factors and SSc has been extensively analyzed. Because those exposures are frequently of long duration, there is growing interest in study of damage to health in the workplace, to establish a safe occupational environment for human health.

The majority of individuals are not aware of the specific agent they have been exposed to during their work, and without validated biomarkers, many of these studies are based on indirect evidence of exposure.

Environmental exposure may vary widely and it may be considered to include all non-genetic factors. Commonly, chemicals or drugs are considered environmental factors; stress events of daily life, other factors from lifestyle and incidental exposures like ultraviolet radiation could also be environmental risk factors for autoinmune diseases. With this in mind, environmental factors can be classificated into 3 categories: occupational, infectious, and non-occupational/non-infectious.

The association between environmental exposure and the beginning of SSc may be difficult to demonstrate. In this situation, the association is rare due to the fact that most of the patients with SSc did not have any exposure, just as the majority of the exposed subjects do not develop the disease, unless we work with a small group of subjects in which both situations occur simultaneously.

Case-control studies are of limited value because of the rarity of the exposure, as are cohort studies because of the rarity of the disease that could develop in an exposed group. Thus, many of these studies do not have enough statistical power to exclude the real effects or to detect moderate associations. The inadequate classification of the type of environmental exposure and other confounding variables may bias the estimated association between exposure and SSc.

Occupational Factors

Silica. The frequency of occupational exposure to crystaline silica dust, as a generator of work damage, has been underestimated, even though it is recognized as a risk factor for many systemic autoimmune diseases including rheumatoid arthritis, scleroderma, systemic lupus erythematosus, and small-vessel vasculitis with renal involvement (antineutrophil cytoplasmic antibody related vasculitis)[38,48-50].

Silicon is an ubiquitous mineral in the environment. It constitutes the second most abundant element in the earth's crust and is part of air pollution particles; it may represent a significant proportion of environmental dust levels in some geographic areas[51,52]. It primarily exists in the crystalline state as quartz, which is structurally and chemically different from amorphous silica (diatomaceous earth), silicates (starch and asbestos), and silicones (a polymer containing silicon: polydimethyl siloxane [$(Si[CH_3]_2O)_n$]). Crystalline silica may be harmful when it is inhalated as respirable dust (particles of less than 5 μm). The allowed limits of exposure for respirable silica stablished by the US Occupational Health and Safety Administration are close to 0.1 mg/m^3 (estimated for an 8 h exposure for quartz), constituting double the recommended limit of exposure: 0.05 mg/m^3, suggested by the US National Institute of Occupational Safety and Health, to minimize the risk of silicosis[53,54].

Professions classically related to occupational exposure to this agent are mining, sandblasting, and pottery. There are many other occupational sources not frequently associated with the induction of autoimmunity. Some examples are mechanical dentistry, agricultural tasks, asphalt work, cosmetology, use of abrasives, jewelry, etc.[50,54] (Table 2)[55].

Technological advances provided powerful tools to the mining industry, increasing the workers' exposure to silica dust. Pneumoconiosis became more frequent and developed faster when steam machinery was installed in factories by the end of the 19th century. The intensive use of pneumatic hammers made this occupation more dangerous for human health[56].

In 1914, a physician from Chalmers Hospital and consultant to the Edinburgh Royal Infirmary named Bramwell described the incidence of scleroderma in 9 Scottish patients. Surprisingly, in his study, there was just 1 female patient[57].

Four decades later, Erasmus expressed his interest in the high prevalence of SSc in 40,013 gold miners from the Witwatersrand[1]. Rodnan, *et al* reported a prevalence study about silica exposure in 60 men with SSc between 1955 and 1965. They showed evidence that SSc in patients with occupational exposure to silica is higher than in the general population, suggesting that silicosis could be a predisposing factor in the pathogenesis of the disease[7].

Other reports documented SSc cases among patients working in mechanical dentistry[58]; a case of conjugal SSc related to silica exposure was also described[59].

In the 1990s case reports, case-control studies, exposure prevalence and incidence studies in patients with Ssc (institutionally or population based) were published. Even though the number of exposed subjects may vary from different samples and the spacio-temporal cluster, the data obtained did not sustain an important role for silica in women, but in some cases evidenced the occupational background of silica exposure for SSc in men (published findings in Tables 3-6)[60-73].

In Argentina, a clinic-based case-control study assessed silica dust exposure in 20 patients with SSc between 1998 and 2002. A questionnaire designed by environmental hygienists was applied to cases and controls discriminating the type of task carried by the subjects: construction, janitorial, agricultural, and dental[72]. Although this study did not achieve adequate statistical power, the group with SSc showed 60% previous exposure to free silica sources [odds ratio (OR) 21; 95% confidence interval (CI) 4.7-101; p <

Table 2. Industries, occupations and tasks with crystalline silica exposure. Data from the International Agency for Research on Cancer[55].

Industry/Occupation	Specific Tasks
Abrasives	Carborundum production; scouring powder manufacture
Agriculture	Mechanical plowing and harvesting; cleaning, sorting, and graving
Agricultural chemicals	Handling and crushing of raw materials
Asphalt and roofing felt	Filling and granule application
Automobile repair	Abrasive blasting
Boiler scaling	Ashes and mineral deposits cleaning of coal fired boilers
Cement	Materials processing: clay, sand, limestone, diatomaceous earth
Ceramics	Mixing, modeling, glazing, enameling and polishing
Construction	Abrasive blasting; highway and tunnel construction; excavation/earth moving; masonry, concrete work, demolition
Mechanical dentistry	Abrasive blasting and polishing
Foundries	Casting, abrasive blasting, felting. furnace installation and repair
Glass and fiberglass	Raw material processing (sand, quartz); refractory installation and repair
Iron, steel mills	Refractory preparation and furnace repair
Jewelry	Cutting, grinding, polishing, buffing (gems and stones)
Metal	Abrasive blasting (structural, machinery, transportation equipment
Mining, milling	Most occupations and mines (ores, associated rock)
Paints	Raw materials handling (fillers)
Quarrying, milling	Stones, sand, gravel processing; stone cutting and abrasive blasting; slate work; diatomite calcination
Rubber and plastics	Materials handling
Ship construction and repair	Abrasive blasting
Silicon-ferro-silicon	Materials handling (sand)
Soaps, cosmetics	Abrasive soaps, scouring powders

Table 3. Studies of SSc in occupational cohorts with silica dust exposure.

Author/location	Methods	Findings
Erasmus, 1957[1], South Africa	Case series (1954–1956); 40, 013 gold miners	17 SSc cases; incidence = 0.04% (18 months)
Sluis-Cremer, 1985[3], South Africa	Case-control (1955–1984); gold miners: 79 cases and 79 age matched controls; exposure: employee records and dust monitoring data by occupation	Difference in cumulative exposure explained by differences in intensity; SSc and silicosis: OR = 1.2 (0.3–5–4)
	Prevalence (1960–1969); members of the Mines Benefit Society; comparison: railway, harbor workers	Gold miners: 28 cases (7.7:100.000); railway/ harbor workers: 3 cases (0.33:100.000)
Cowie, 1987[60], South Africa	Incidence: (1981–1986); gold miners:24.450 Comparison: 486 age-matched miners Exposure: history by questionnaire	10 cases (8.2:100.000/yr) No difference in percent with silicosis, exposure years or intensity
Sánchez Román, 1993[5], Spain	Prevalence: (dates not specified—10 yrs); –300 scouring powder factory workers; Sample: 50 volunteers (88% female)	5 cases (1.667:100.000)
Melhorn, 1999[61], Eastern Germany	Incidence: (1966–1995); uranium miners (male); 243.000 highly exposed, including 12,400 silicosis cases 50,000 low exposed Comparison: estimated population rates of silicosis and SSc (0.2:100.000/yr)	Total high: 94 cases; RR = 7.8 (6.5–9.5); with silicosis: 60 cases; RR = 97 (75–125); without silicosis: 34 cases; RR = 3.1 (2.2–4.3) Total low: 3 cases; RR = 1.2 (not significant

SSc: systemic sclerosis; RR: relative risk; OR: odds ratio. Modified from Parks, *et al*[54].

10^{-7}]. Sixty-seven percent of patients with SSc and silica exposure were women (OR 24.6; 95% CI 3.6-216; $p < 10^{-5}$). Time of latency between the beginning of the exposure and disease diagnosis was 21 years, on average. In an emerging country, the role of women in tasks classically assigned to men may be similar in middle and low income classes.

Vinyl chloride. This is an uncolored combustible gas (CH2 = CHCl), used in plastic manufacturing. In the mid-1960s a new syndrome affecting workers of vinyl chloride polymerization was described by Wilson and colleagues[74]. These patients developed finger paresthesias, Raynaud's phenomenon (RP), pseudo-acropachy, skin thickening, edema of hands and forearms, and chest radiographic changes[75]. Risk for suffering these alterations is related to cumulative exposure over time and not necessarily with manipulation of the

Table 4. Registry-based studies on occupational exposure to silica dust or silicosis and autoimmune disease-SSc.

Author/location	Methods	Findings
Rosenman, 1995[48], Michigan, USA	Hospital discharge diagnosis (1990–91); 160 patients with silicosis; 355 coal worker's pneumoconiosis; 252 asbestosis; 67 unspecified dust exposure Comparison: all other discharge diagnosis	No cases of SSc and pneumoconiosis
Steenland, 1995[62], South Dakota, USA	Mortality (1940-91); 3.328 gold miners; multiple-cause mortality listing Comparison: South Dakota population	MSK: (SLE/SSc) SMR: 2.1 (1.0–3.9); skin: (SLE/SSc) SMR: 2.4 (1.2–4.5); SSc:
Brown, 1997[63] Sweden and Denmark	Hospital discharge diagnosis; Sweden (1965–83); Denmark (1977–89); Discharge diagnosis of silicosis Comparison: all other discharge diagnoses	5 cases: RR = 37 (11.9–86.3)
Walsh, 1999[64], USA	Mortality (1985–92); death certificates from 25 states; death from SSc or from silicosis Exposure: 37 occupational groups Comparison: other occupations	SSc (men): OR = 1.0 (0.8–1.2); SSc (women): OR = 0.8 (0.6–1.2)
Rosenman, 1999[49], Michigan, USA	Prevalence (1985–95); 463 silicosis cases from state registry system; medical records review and questionnaire	SSc: 1 case (0.2%) OR = 15.6 (0.2–87)
Calvert, 2003[65], USA	Mortality (1982–1995); death certificates from 27 states with data from occupational databases of the NOMS; silica-related disease listing from the ICD	SSc: 2875 cases; with silicosis: 2 cases; without silicosis: 5 cases
	Exposure: evaluation by environmental higienists according to the NIOSH Comparison: 5 controls (without silica-related disease) for each case, age, sex, region and year of death matched	MOR = 2 (0.4–10.3)

SSc: systemic sclerosis, MSK: musculoskeletal disease, SMR: standardized mortality ratio, SLE: systemic lupus erythematosus, RR: relative risk, OR: odds ratio, MOR: mortality odds ratio, NOMS: National Occupational Mortality Surveillance, ICD: International Classification of Diseases, NIOSH: National Institute for occupational Safety and Health.

Table 5. Case-series studies describing silica exposure in SSc.

Author/location	Methods	Findings
Rodnan, 1967[7], Pennsylvania, USA	Exposure prevalence (1955–65); 60 cases—males Exposure: prolonged heavy silica exposure	26 exposed cases (43%)
	Exposure prevalence: (1955–65); 43 hospitalized male cases; 86 age, sex and race-matched hospital controls Exposure: prolonged heavy silica exposure	20 exposed cases (47%) 16 exposed controls (19%)
	Hospital discharge diagnosis: (1958–62); 10 hospitals (Appalachian region) Exposure: coal min workers	11 male cases, 9 female cases miners (males): 17:100,000; non-miners (males): 6:100,000; non-miners (females): 9:100,000
Koeger, 1995[38], France	Exposure prevalence (1979–89); 764 hospitalized cases: 118 SSc Exposure: assessment of works held ≥ 3 years	8 exposed cases (6.7)
Ziegler, 1997[66], Eastern Germany	Exposure prevalence (1971–91); 54 SSc male cases (not uranium miners) Exposure: assessment of job history Comparison: population estimates of exposure prevalence (< 10%) and silicosis (< 1%)	24 cases (44%) exposed to dust > 20% quartz; 5 cases (9%) exposed to dust > 5% quartz; OR = 10.4 (6.1–17.8) with silicosis: OR = 25.3 (13.0–49.1); Without silicosis: OR = 6.2 (3.4–11.5)
Haustein, 1998[67], Eastern Germany	Exposure prevalence: (1980–97); 137 male and 454 female cases Exposure: self-reported history of silica-related work held ≥ 6 months	Male cases: 111 (81%) exposed; female cases: 7 (1.5%) exposed
Magnant, 2005[68], Tours, France	Clinic-based (1998–2002); 17 male cases and 88 female cases Exposure/occupation: structured interview about jobs held > 6 mos	16 silica exposed cases p = 0.10

SSc: systemic sclerosis. OR: odds ratio. Modified from Parks, et al[54].

final product, polyvinyl chloride (PVC)[74]. There seems to be an apparent increase of the prevalence of MHC DR3 and DR3/B8 haplotypes in patients with this disease[76]. Skin changes in vinyl chloride disease may be similar to morphea, and the most striking hallmark of the syndrome is phalanx acroosteolysis[75]. Several immune alterations have been

Table 6. Case-control studies on silica exposure and SSc.

Author/location	Methods	Findings
Silman, 1992[69], United Kingdom	Clinic based (dates not specified) 56 male cases 56 age, sex and clinic-matched controls 41 age and sex-matched friend-controls Exposure: assessment of jobs (length not specified) and self-reported exposures	No cases with probable silica exposure 2 cases with probable silica exposure Clinic controls: OR = 1.0 (0.1–7.2) Friend controls: OR = 1.4 (0.1–16.1)
Bovenzi, 1995[70], Italy	Clinic based: (1976–91) 21 cases (5 men, 16 women)Women: no exposed cases 42 age and sex matched clinic controls Exposure: Assessment of all jobs held ≥ 6 mo	Men: OR = 5.2 (0.48–74.1)
Burns, 1996[71], Michigan, USA	Population based: (1985–91) 274 female cases, 1184 age, sex and region-matched controls Exposure: assessment of jobs held ≥ 3 months/history of jobs held ≥ 5 yrs	Working with/around silica: OR = 1.5 (0.7–2.9) Grinding, pottery, dental lab: OR = 1.2 (0.8–1.9)
Englert, 2000[13], Australia	Population based; 160 male cases; 83 age and sex-matched controls	OR = 3.93 (1.84–8.54); OR = 2.51 (1.28–4.98), (adjusted by socioeconomic level)
Australia, Edenhope, 2005[27]	Population based: (1991) 5035 men, 4795 women; 2 age, sex and region-matched controls per case Comparison: SSc estimated prevalence in the population Exposure/occupation: phone survey about work held > 6 mos	6 SSc cases; prevalence = 6.1/10,000; RR = 10.2 (4.5–23)
Mora, 2003[72], Argentina, Buenos Aires	Clinic based: (1998–2002); 20 patients (15 women, 5 men); 61 sex and age-matched controls Exposure: structured questionnaire designed by environment hygienists about silica-related tasks held > 6 mos	12 exposed cases/4 exposed controls; OR = 21 (4.7–21); 8 female exposed cases; OR = 24.6 (3.6–216); 4 male exposed cases; OR = 28 (1.4–1200)
Bovenzi, 2004[73] , Italy	Clinic based: (1997–1999); 46 women, 9 men; 153 sex and age-matched controls Exposure: structured questionnaire assessed by an environmental hygienist about work held > 6 mos	8 exposed cases (5%)—2 women, 1 man; 5 exposed controls (3%)—3 women, 2 men; OR = 1.7 (0.4–7.6)

SSc: systemic sclerosis. OR: odds ratio. Modified from Parks, et al[54].

described, such as polyclonal IgG increase, cryoglobulins, complement activation, and antinuclear antibodies (ANA) in low titers[10]. Clinical and symptomatic improvement after withdrawal of the exposure is characteristic[74].

Organic solvents. The determination of the type of solvent that a subject has been exposed to is crucial to the accuracy of epidemiological studies. It is frequently difficult to infer which agent is involved, not only because of limitations in the individual's knowledge but also because frequent users of solvents do not look for a specific chemical but for the chemical properties of solvents or their blends. Examples of them are trichloroethylene (TCE), perchloroethylene (PCE), toluene, paint thinners, varnish, gasoline, and aromatic hydrocarbons[77].

Estimations of industrial exposure to solvents may widely vary depending on the type of use or industry. Domestic exposure and use of solvents in hobbies such as cleaning, and furniture and ship restoration are even more variable due to differences in ventilation, lack of training in solvent use, absence of legal regulations, and the idiosyncratic nature of working habits of people in their homes[77].

Exposure levels in Table 7 represent the upper limit of typical exposures for these agents in several situations, more than their whole rank. These levels could vary from high to trace (Table 7). Some high level exposures are from historical records and they should not happen within the present regulatory framework.

The American Conference of Governmental Industrial Hygienists recommended a maximum level of exposure for an 8 h exposure for each type of solvent. These recommendations (threshold limit value) for average exposure of 8 h are concentrations in the environment's aerosol not believed to have serious consequences on adult health[77]. Exceeding these limits is not prohibited by any regulatory authority, but they are recognized as reasonable limits in many countries.

The first description of TCE induced SSc reported a group of German workers in 1957[78]. Years later, Walder referred to the association of exposure to solvents and the development of SSc[14].

In 2007, Kettaneh, *et al*'s metaanalysis of case-control studies about occupational exposure to solvents and the sex-related risk of SSc (Figure 1)[79-86]. They stated that occupational exposure to solvents confers an increased risk of SSc to men [OR 3.0 (1.9-4.6), $p < 0.0001$] compared to women [OR 1.8 (1.5-2.1), $p < 0.0001$].

Other agents. In 1977 Fessel published 2 cases of SSc in the context of an intense professional exposure to welding fumes[87]. In 2002, Diot, *et al* stated that an existing exposure

Table 7. Typical uses, upper range of reported exposure levels and recommended exposure limits for solvents associated with connective tissue diseases.

Solvent	Industrial use	Exposure level (mg/m^3)	SCGIH-TLV (mg/m^3)
Benzene	petroleum derivate (a compound of gasoline	0.1–27.2	1.6
Toluene	Tire vulcanization	5.66	1.88
	Leather finishings	735	
	Hospital laboratory	47.5	
	General manufacturing	452	
Xylene	Hospital laboratory	1700	434
	General manufacturing	61	
Trichloroethane	Nonflammable cold cleaning solvent; used alone or blended	Not typically used in consumer products	1900
Trichloroethylene (TCE)	Nonflammable liquid that dissolves fat, grease, tar or waxes; used for cold cleaning		269
	Degreasing	4833	
	Typographic correction fluid		
Perchlorethylene (PCE)	Nonflammable liquid used in cold cleaning, where slow evaporation is desired		170
	Degreasing	12204	
	Dry cleaning	3899	
Varnish and paints, naphta	Paint thinner with 100-160°C boiling point		1370

ACGIH: American Conference of Governmental Industrial hygienists; TLV: threshold limit value[71].

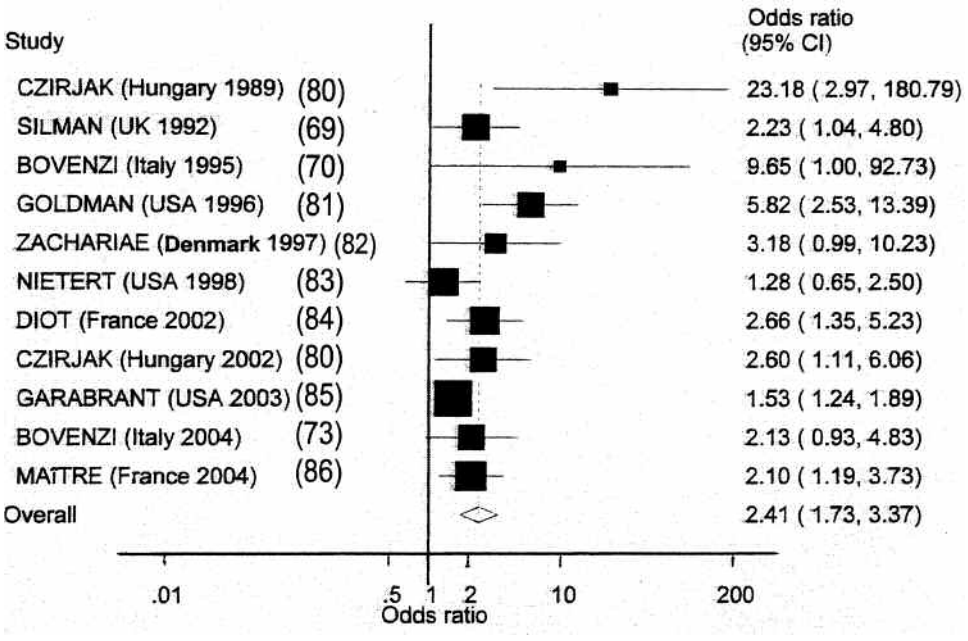

Figure 1. Metanalysis of Kettaneh and colleagues[79] on exposure to any organic solvent and risk of systemic sclerosis in the whole sample. Points and diamond represent the odds ratio (OR) with 95% confidence interval (CI). The size of each box is approximately proportional to the weight of the study in the metaanalysis.

to these fumes could carry an OR of 3.74 (1.06-13.18) for SSc[84].

Exposure to vibrations is considered a risk factor for SSc due to case reports of patients using vibrating tools in their professional work[88,89]. In 2001 Bovenzi, *et al* carried 2 case-control studies to verify this occupational hypothesis. The OR obtained in each study were not significant[90]. The study of Maitre, *et al* in 2004 depicted an OR of 3.9 (0.8-19), statistically nonsignificant due to the limited number of exposed cases[86].

The process of industrial polymerization of epoxy resins has been associated in several reports with skin sclerosis, arthralgias, and myalgias, but not with visceral involvement nor with RP or autoantibodies[16]. Silman and Jones studied a

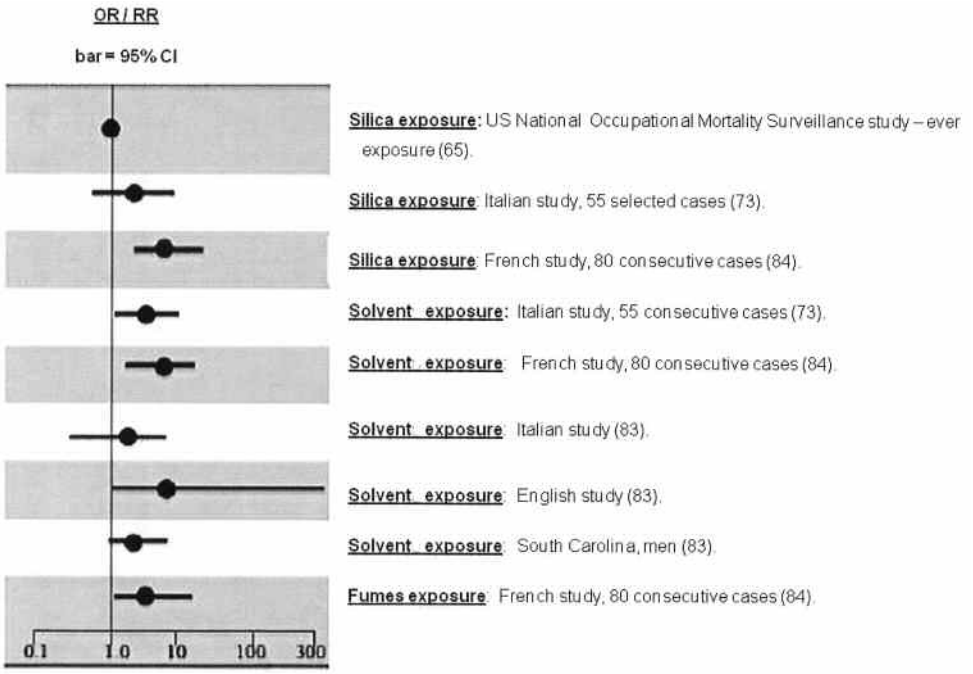

Figure 2. Epidemiologic studies regarding non-occupational/non-infectious factors and systemic sclerosis.

population of 56 men with SSc and found an OR of 1.7 (0.4-7.3) on exposure to epoxy resins[69]. The limited number of studies and the heterogeneity of the results do not permit assigning a role as a risk factor for these substances.

Infectious Factors

Bacterial and viral infections have long been considered as contributing factors to the development and progression of SSc. This hypothesis could be sustained by the fact that many sclerodermiform symptoms are transiently provoked by infectious agents in healthy subjects[91].

Bacterial agents. There are 2 lines of evidence involving bacterial infection in the pathogenesis of SSc. One of them is anecdotal evidence that antibiotic therapy ameliorates SSc symptoms in some people. The other is evidence that graft versus host disease (GVHD), which shares many features with SSc, cannot be induced in "aseptic" animals[92,93] and its incidence is significantly reduced in childrent pretreated with antibiotic to eradicate their normal bacterial flora[94].

Helicobacter pylori (HP) is a gastric bacterium that has been involved in some vascular disease[95] and has been studied as a potential risk factor for SSc. In a study of patients with primary RP, eradication of HP infection with a triple antibiotic schedule was associated with disappearance of RP in 17% of treated patients and a decrease of symptoms in another 72% of subjects[96]. Although this was not a double blind trial, it is interesting to observe the lack of improvement in those patients in which HP infection was not completely eradicated. Another study of comparable design reported similar results[97].

Attempts to associate HP infection and SSc have yielded conflicting results. One study identified high incidence rates of infection in patients with autoimmune disease, such as SSc[98]. In contrast, 2 studies found no differences in HP infection rates between patients with RP and SSc and healthy controls[99,100]. Although is true that the rates of HP infection do not correlate with SSc, this does not rule out its role in the disease[101]. There is evidence that HP infection is not different between patients with SSc and healthy controls, but it has been shown that 90% of patients with SSc were infected with the HP strain CagA, in comparison with 37% of infected controls[101]. For this reason, confounders like co-infections, differences between HP strains, and host factors should be observed and controlled to understand HP's role in RP and SSc.

Viral agents. SSc is also associated with viral infection. The pathogenic role of 2 viruses, HCMV and parvovirus B19 (B19), has been recently proposed. Herpes viruses, in particular HCMV, have been involved in several vascular diseases including atherosclerosis, allograft rejection vasculopathy, vascular restenosis, and GVHD.

Neointimal formation is a common feature shared by SSc and all the above vascular diseases. When human cytomegalovirus (HCMV) infects vascular endothelium and this process is characterized by latency, reactivation, and spreading of viruses to distant tissues. In murine models it was shown that CMV infection leads to the development of intimal lesions[102,103]. There is indirect evidence of a HCMV role in SSc, linking high levels of HCMV antibodies and the prevalence of specific SSc autoantibodies in patients with

scleroderma[104-106]. Recently, molecular mimicry mechanisms have shown a relationship between antibodies against the HCMV derived protein UL94 and SSc pathogenesis[106]. UL94 epitope shares homology with NAG-2, a surface molecule highly expressed in endothelial cells. Antibodies against UL94 purified from sera of patients with SSc induce endothelial cell apoptosis by enhancing a NAG-2/integrin complex. NAG-2 is expressed in dermal fibroblasts and anti-UL94 bind to fibroblasts activating them, with subsequent fibrosis.

HCMV infection and its downstream effects on immune, vascular, and repairing effects serve as a trigger for SSc. The identification of genes controlling susceptibility to CMV in mice by genetic analysis may be a path to understanding human genetic susceptibility to HCMV infection.

Strain C57BL/6 mice, genetically resistant to CMV, do not develop vascular pathology in response to the infection, while susceptible mice (129 interferon R-/-) develop neointimal lesions that reproduce CMV infection in a dose dependent manner[107].

Microchimerism is another possible mechanism to explain sporadic development of SSc regarding its 8:1 rate of women/men affected by the disease. Microchimerism refers to prolonged allotypic lymphocyte survival (fetal T cells acquired during pregnancy or cells received by transfusion or organ transplant), usually in circulating blood. Fetal microchimeric T cells were isolated 27 years after delivery in a patient with SSc, and it has been shown that they are more common in patients with SSc than in age matched healthy controls[108]. Pathogenic effects of these cells are unknown, but microchimeric cells were also found in cell infiltrates of scleroderma lesions[109]. Engraftment and survival of these cells depends on the complex relationship between tissue antigens from the mother and the fetus (or host and donor), and so, they are highly variable[110].

In vitro studies showing T cells exposed to allotypic endothelial cells activate and proliferate more if they are infected by HCMV, sustaining the idea that HCMV can induce proliferation of microchimeric cells[111].

Vascular endothelium is an allotypic stimulus for circulating microchimeric cells. If endothelium is infected with HCMV, cytokine production may be amplified, possibly triggering endothelial cell activation, vascular inflammation, and neointimal formation such as it happens with T cells transplanted in GVHD.

Genomic sequences of B19 have been found in 57% (12/21) of bone marrow specimens from patients with SSc and in none of the control group. It has been speculated that bone marrow could be a reservoir of the virus from which viruses disseminate to target tissues in SSc[112]. There was also an increase in the frequency of anti NS1-B19 antibodies in sera of patients with SSc (33%) compared to controls (13%).

In a case series, ANA with a nucleolar pattern were detected in a patient with B19 arthritis[113].

Altschuler[114] highlighted that SSc is a relatively new disease, with the first case reported in 1753[115], coincidental with the B19 virus reintroduction in Europe (in the XVI century).

Non-occupational/Non-infectious Factors

There are few epidemiologic studies regarding such factors and SSc, even though there is a wide list of them (Figure 2).

Drugs — estrogens. Beebe, *et al*[116] studied the association between reproductive history, oral contraceptives, and estrogen replacement therapy in 472 women with SSc and 2227 controls. They did not find a relationship between risk of Ssc and contraceptive intake, early menarche, or multiple delivery. Hormone replacement therapy with estrogens showed an association with a mild but significant increase of SSc, with an adjusted OR of 1.40 (1.10-1.77). Mean age at start of therapy was not different between cases and controls, suggesting that early menopause did not cause the results.

Fraenkel and colleagues[117] assessed the association between estrogen replacement therapy and RP in 497 postmenopausal women in the US Framingham Offspring Study. RP prevalence was 8.4% in women not receiving treatment, 19.1% of those receiving estrogens and 9.8% of women taking estrogens plus progesterone. Adjusted OR was 2.5 (1.2-5.3) for estrogens and 0.9 (0.3-2.6) for estrogens plus progesterone. This risk was associated with development of the disease after initiation of treatment, and does not necessarily imply a worse prognosis by their intake itself[118].

Appetite suppressants. There are a few case reports documenting SSc after prolonged use of these drugs. Examples of them are dexamphetamine, diethylpropion, fenfluramine, fenproporex, mazindol, methaqualone, and phenmetrazine[119]. Duration of therapy, variety of drugs used, and lack of prescription criteria in the general population make it difficult to analyze if there is a chance of co-occurrence or if it is a real phenomenon.

Carbidopa and L-5 hydroxytryptophan (5-HTP). Carbidopa inhibits conversion of 5-HTP to 5-hydroxytryptomen and the alternative pathway to tryptophan metabolism leads to an increased synthesis of quineurin. High levels of this molecule are associated with SSc, and this is not observed in patients continuously treated with carbidopa/L-5HTP.

A patient receiving carbidopa as treatment for myoclonus developed SSc after therapy[120].

Bleomycin. Bleomycin is an antitumoral antibiotic drug used for several types of cancer, primarily isolated from *Streptomyces verticillus*[121]. Lung fibrosis is a known side effect of this drug. Skin changes like hyperpigmentation, alopecia, gangrene, edema, RP, fibrosis, scleroderma, and others were described in relation with bleomycin[122].

Bleomycin induced lung fibrosis is an established murine model, pathologically and biochemically similar to human

lung fibrosis. Mice develop acute alveolitis followed by an intense interstitial inflammation when bleomycin is administered intratracheally. Late in its evolution, there is an increase of the extracellular matrix (collagen, fibronectin, hyaluronates, and small proteoglycans)[123,124].

In vitro, this drug upregulates collagen messenger RNA in the lungs and dermal fibroblasts[125,126]. Mountz, *et al* reported that mice repeatedly injected with sublethal doses of bleomycin develop severe dermal fibrosis — similar to human SSc — in a 58-week period, with structural anomalies in collagen fibers[127].

Five cases of scleroderma-like disease following bleomycin use were described in 2 case reports[18,128]. Bleomycin use enhanced an *in vivo* lymphoproliferative response in one of these patients[18].

Gadolinium. Nephrogenic systemic fibrosis (NSF)[129] was described in 2000[130]. This entity is characterized by extensive cutaneous fibrosis similar to SSc, sparing the face and neck in the absence of autoantibodies, also involving lungs, heart, liver and muscle[131].

A link with contrast agents containing gadolinium was first established in 2006[132], leading regulatory bureaus to set recommendations for its use. In 2007, the US Food and Drug Administration warned health professionals to avoid gadolinium use in patients at risk of developing NSF, to evaluate renal function, not to exceed the dose recommended on the product label of this substance, and eventually, to consider immediate hemodialysis after infusion of a gadolinium-containing agent[133].

Other drugs. Cases of cutaneous sclerosis proven histologically — even without clinical features of Ssc — have been described in relation to pentazocine abuse[21].

A few articles have linked cocaine abuse with SSc development in young men[134,135]. Cocaine causes vasoconstriction, and may constitute a first step in the pathogenesis of SSc in a susceptible host.

Mercury chloride is an immunomodulating agent that may cause immunocomplex mediated glomerulonephritis and autoantibody production in susceptible mice strains[136,137]. These autoantibodies recognize the fibrillar protein fibrillarin[138]. Arnett, *et al* suggested that mercury modifies fibrillarin, causing autoantigenicity[139]. Anti-fibrillarin antibodies are found in 8% of patients with SSc and are associated with severe forms of the disease.

Pesticides. There are potential endocrine modulators under the form of pesticides that could also increase the risk of SSc. Some pesticides are known as endocrine disruptors, like polychlorinated biphenyls (PCB), DDT metabolites, and 2.3.7.8-tetrachlorinedibenzo p-dioxin (TCDD).

PCB exert an anti-estrogen effect by inhibition of estrogen-mediated transduction signals[140,141]. Similarly, a DDT metabolite (p,p-DDE) may bind the aryl-hydrocarbon receptor, which plays a role in hormone signaling[142]. Acute and chronic exposure of mice to TCDD affects their bacterial pathogen innate immunity by supressing total hemolytic complement and C3[143].

A case of SSc was documented after exposure to a combination of herbicides: bromobuthyl-methyluracil, dichlorophenyl-dimethylurea, and aminotriazole[144]. Aminotriazol may cause contact dermatitis[145], but none of these compounds was previously associated with autoimmune diseases. In a case-control study in women, exposure to pesticides and herbicides by self-reference showed an adjusted OR of 2.19 for SSc, without distinction between both exposures[146].

Silicones. These are synthetic polymers with organic groups bound to silicone atoms by carbon-silicon bonds; polydimethyl siloxane is the most commonly used silicone in medicine[147].

Silicone gel has been used since 1962 to fill breast implants[118]. Silicone elastomer containing chemically treated amorphous silica is added to the capsule of certain breast augmentation implants to increase its tensile strength, reducing the potential of implant rupture[148].

The first report of a connective tissue disease related to silicone was in a young woman who received silicone injections for breast augmentation[149]. Other reports referred to this circumstance as "adjuvant induced disease"[150].

Association between silicone breast implants and the occurrence of SSc was not observed in several epidemiological studies[71,151-154]. The risk for SSc in implanted medical devices was also evaluated[71] but this study did not find an association.

CONCLUSIONS

Understanding the link between environmental risk factors and the development of SSc is limited due to the phenotypic and pathogenic heterogeneity of the patients and the disease, respectively, and also because there is a poor ability to assess environmental exposures quantitatively and the role of gene-environment interactions in this disease.

Global collaboration could allow better use of the data obtained from a limited number of cases and limited resources. Collaboration may exploit the natural genetic and environmental variability on the planet, together with a careful phenotyping of larger populations of patients with SSc and the development of larger and more detailed databases. Normalization and validation of biomarkers and questionnaires could also be very useful to reliably quantify environmental exposures.

The use of genomic techniques to assess exposure biomarkers through their RNA expression signatures, proteomic, metabolomic, and microarray studies could change our ability to define environmental risk factors in the future. Even though those approaches require additional research and the use of resources for a long period, the investment should be made in terms of cost-effectiveness to provide an

accurate understanding of disease mechanisms and to evolve to a predictive, personalized, and preventive medicine.

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