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REVIEW

Environmental risk factors of systemic sclerosis

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Abstract Systemic sclerosis (SSc) has a complex pathogenesis. Although, there is a growing evidence that environmental factors have an impact on alterations and modulation of epigenetic determinants, resulting in SSc onset and progression. A marked correlation has thus been found between SSc onset and occupational exposure to crystalline silica and the following organic solvents: white spirit, aromatic solvents, chlorinated solvents, trichloroethylene, and ketones; the risk associated with high cumulative exposure to silica and organic solvents further appears to be strongly increased in SSc. Altogether, occupational exposure should be systematically checked in all SSc patients at diagnosis, as (1) exposed patients seem to develop more severe forms of SSc and (2) the identification of the occupational agents will allow its interruption, which may lead to potential improvement of SSc outcome. By contrast, based on current published data, there is insufficient evidence that exposure to other chemical agents (including notably pesticides as well as personal care such as silicone and hair dye), physical agents (ionizing radiation, ultraviolet radiation, electric and magnetic fields), and biological agents (infections and diet, foods, and dietary contaminants) is a causative factor of SSc. Further investigations are still warranted to identify other environmental factors that may be associated with SSc onset and progression.

Keywords Systemic sclerosis · Epigenetics · Environmental factors · Occupational factors · Crystalline silica · Solvents · Trichloroethylene · Ketones · Welding fumes · Pesticides

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Introduction

Systemic sclerosis (SSc) is a systemic inflammatory disorder affecting the skin and other organs [1–4]. The condition is characterized by three histopathologic features: (i) both structural and functional vascular lesions, associated with progressive endothelial damage, reduction in the number of capillaries, thickening of arterial walls, and obliterative vasculopathy; (ii) perivascular and tissue infiltration of mononuclear inflammatory cells at early stages of SSc [5–8] (histological analyses of skin biopsy specimens have shown prominent CD4+ cellular infiltration with overexpression of cellular adhesion molecules in both vessels and interstitium); and (iii) increased synthesis and excessive deposition of extracellular matrix, resulting in fibrotic destruction of internal organs during the course of SSc [5–8].

The pathogenesis of SSc still remains unclear, although it is increasingly thought to result from interactions between environmental factors and epigenetic features leading to the onset and progression of SSc in genetically susceptible patients. To date, it is established that epigenetic modifications are characterized by both stable and heritable changes in gene expression without modifications to the original DNA sequence [5, 9–11]; thus, three main epigenetic features are thought to determine the epigenome in SSc, i.e.,

- *DNA methylation*, leading to dysregulation of many cells, including principally (1) CD4+ T cells which seem to be hypomethlylated. CD4+ T cell hypomethylation has been shown to be associated with reduced expression of methylation-regulating genes: DNA methyltransferase-1 (DNMT1), methyl-CpG-binding domain (MBD) 3, and MBD4 [6, 9, 12]. Furthermore, CD40L gene promoter has been shown to be hypomethylated and transcriptionally active in CD4+ T cells [6, 9, 13]. In female SSc patients, the presence of demethylated CD40L regulatory elements on the inactive X chromosome leads to CD40L overexpression; these latter findings may, in part, explain the predominance of SSc in females [6, 9, 13]; (2) endothelial cells from SSc patients have been found to show CpG hypermethylation of the bone morphogenetic protein receptor factor type 2 (BMPR2), which may contribute to higher vulnerability of endothelial cells to apoptosis and oxidation damage [14]. Additionally, CD70 is part of the tumor necrosis factor (TNF) α superfamily and is restricted to T and B lymphocytes and mature dendritic cells [6, 9, 10]; in SSc patients, the promoter of CD70 is hypomethylated, leading to the overexpression of CD70 by CD4+ T cells; and (3) fibroblast global DNA hypermethylation has been found in dermal fibroblasts from SSc patients; histological analyses of skin biopsy specimens of SSc patients showed higher levels of methylation regulatory genes DNMT1, MBD1, and methyl-CpG-binding protein (MECP) 2 than controls [6].
- *Histone modifications*, contributing to impairment in (i) transcription of genes and (ii) modulation of gene expression [6, 9]. Transforming growth factor β (TGF-β)-induced transcription of fibrotic genes is markedly dependent on histone acetylation catalyzed by acetyltransferases, including p300 [15, 16]. In experimental models of skin/lung fibrosis and in SSc skin biopsy samples and explanted fibroblasts, analyses have shown elevated lesional tissue p300 levels, promoting histone H4 hyperacetylation and collagen transcription [16]. Furthermore, the histone deacetylase sirtuin 1, which exerts antifibrotic effects by blocking Smad-dependent transcription, has been found to be reduced in human and mouse fibroblasts in culture as well as murine model of fibrosis [16].
- *MicroRNA profile*, resulting in a pro-fibrotic process [5, 6, 9, 10, 17]. Previous investigators have shown that SSc patients, compared with healthy subjects, had (1) ex vivo lower levels of miR-29 (which has a master antifibrotic action on collagen I and III and extracellular matrix components via inhibition of expression of COL1-A1, COL1-A2, and COL1-A), which suggests an association with TGF-β and platelet-derived growth factor β (PDGFβ) pathways [6, 10, 18, 19]; (2) higher values of miR-92a in dermal fibroblasts and in sera, resulting in reduced metalloprotease 1 [6]; (3) decreased levels of miR-129-5p in dermal fibroblasts, leading to increased expression of collagen I and connective tissue growth factor (CTGF) [20]; and (4) higher serum levels of miR-143-3p, which were predictive of SSc severity [21].

To date, there is a growing evidence to underscore the effect of environmental factors on alterations and/or modulation of epigenetic determinants (DNA methylation, histone modifications, and microRNA profiles), resulting in SSc onset and progression [5, 6, 9, 21]. Therefore, many environmental factors have been incriminated to play a role in SSc pathogenesis, which can be divided into (1) chemical agents, including notably occupational chemical agents; (2) physical agents, including ionizing radiation, ultraviolet radiation, and electric and magnetic fields; and (3) biological agents, such as infections, foods, and dietary contaminants. The aim of the present article is thus to review the association between these environmental factors and both SSc onset and progression.

Chemical agents

In our review, the association between SSc risk and the following chemical agents has been evaluated: silica, asbestos, organic solvents, other industrial chemicals, pesticides and persistent organic pollutants, air pollutants, smoking and drug abuse, as well as personal care.

Silica

Freshly fractured particulate silica (crystalline silica, quartz) is released in gold mining, sandblasting, rock drilling, sand factory work, granite cutting, construction work, brick laying, sail tilling, cement work, and scouring powder factory work (Table 1) [2, 4].

Bramwell [22] was the first to describe SSc in Scottish stonemasons. In 1957, Erasmus [23] has reported a higher incidence of SSc in gold miners exposed to crystalline silica, compared with the general population (2/1000 vs. 0.35/1000). Previous case–control series have found a correlation between crystalline silica and SSc [23–28]. Haustein et al. [29] have mentioned that SSc risk, for crystalline silica-exposed subjects, was 25 to 50 times that of unexposed subjects. In a case–control study (80 patients, 160 controls), the authors have found an association between silica exposure and SSc (OR 5.57, 95 % CI 1.60 to 18.37); the risk was elevated in patients with high level (>1) of crystalline silica exposure (OR 3.74, 95 % CI 1.06 to 13.18) [25]. Moreover, a 2012 meta-analysis of 16 series (total 1101 cases in 3 cohorts and 9 case–control series) demonstrated that SSc patients were more often exposed to crystalline silica (OR 3.20, 95 % CI 1.89 to 5.43); the risk appeared to be higher in men (OR 3.02, 95 % CI 1.24

Table 1 Occupations associated with exposure to crystalline silica

- Work of drilling, demolition, extraction, and transport of ores or rocks containing free silica
- Crushing, grinding, sifting, and handling carried-out dry ores or rocks containing free silica
- Cutting and polishing of rocks containing free silica
- Manufacture and handling of grittings, scouring powders, or other products containing free silica
- Work of sanding and dry sawing of materials containing free silica
- Work in the coal mines
- Extraction, splitting, cutting, smoothing, and polishing of slates
- Use of crushed slate dust in rubber factory or in the preparation of cement or sinter
- Extraction, crushing, and conditioning of talc
- Use of talc like lubricant or like charges in paper sizing, certain paintings, preparation of cosmetic powders, and mixtures of rubbers
- Manufacture of carborundum, glass, porcelain, earthenware, and other products such as ceramics and refractory products
- Work of foundry exposing to dust of sand, stripping, trimming, and desanding
- Work of grinding, polishing, and dry grinding by means of grinding wheels containing free silica
- Work of scouring or polishing to the sand blast
- Building work and demolition exposing to the inhalation of dust containing free silica

to 7.35) than in women (OR 2.03, 95 % CI 0.74 to 1.44) [30]. Finally, in a 2014 case–control study, a marked association between SSc and crystalline silica exposure (OR 5.32, 95 % CI 2.25–13.09) has been reported; although, there was a significant association between SSc and crystalline silica exposure only in male patients (OR 8.30, 95 % CI 2.58–29.60) [2]. Additionally, the risk was higher in male SSc patients with high level (cumulative exposure score >1) of crystalline silica exposure (OR 9.63, 95 % CI 2.49 to 43.01); the risk was further stronger in patients with very high level (cumulative exposure score >5) of crystalline silica exposure in overall SSc patients (OR 9.68, 95 % CI 2.14–59.43) [2]. In this study, most of SSc patients exposed to silica were foundry workers, building workers, and roofers [2]. Furthermore, a case report of limited cutaneous SSc has also been described in a winegrower, who commonly filtrated wine using calcined diatomaceous earth (i.e., diatoms are microscopic plants extracting silica from lakes/seas), containing 90 % pure crystalline silica [31].

Interestingly, occupational exposure to crystalline silica has also been found to be a predictive parameter of SSc severity [4, 25]. In a previous series, the authors reported that SSc patients, who exhibited exposure to crystalline silica, compared to non-exposed SSc patients, developed more frequently (i) diffuse cutaneous SSc (P=0.02), higher value of modified Rodnan score (P=0.001), digital ulcers (P=0.05), lower median value of left ventricular ejection fraction (P=0.006), and (ii) interstitial lung disease (ILD) (P=0.0004) [4]. ILD was also more severe in the group of silica-exposed patients with SSc who exhibited lower median values of forced vital capacity (FVC) (P=0.004), vital capacity (VC) (P=0.001), and diffusing capacity of the lungs for carbon monoxide (DLCO) (P=0.01) on pulmonary function tests and more commonly honeycombing (P=0.045) pattern on HRCT scan [4].

The pathogenic mechanisms of crystalline silica remain unclear in the development of SSc. Because silica is a strong T cell adjuvant, dysregulated immune response triggered by crystalline silica in genetically predisposed subjects could lead to tissue damage and systemic inflammatory response [32]. Experimental series have indicated that silica, administered intratracheally or intravenously, may interact with alveolar macrophages leading to immune dysfunction and notably to (1) activation of T and B lymphocytes, resulting in cytokine synthesis (TNF, interleukin-1b, TGF-β) and autoantibody production; (2) autoimmunity related to apoptosis with autoantigen alterations [33] (when neutrophils undergo apoptosis, primary granule constituents translocate to the cell surface, leading to both generation of self antigens and tolerance breakdown [34]); and (3) activation of fibroblast proliferation, with increased synthesis of collagen and other components of extracellular matrix (fibronectin, glycosaminoglycans) [2, 30]. In addition, chronic exposure to silica has been reported to activate both responder T cells and regulatory T cells [32, 35, 36]. These activated responder T cells enter the peripheral CD4+25+ fraction and activated regulatory T cells, which may result in reduced inhibitory function of regulatory T cells [32, 35, 36]. Furthermore, persistently activated responder T cells may also express Fas-mediated apoptosis inhibitory molecules such as soluble Fas and survive longer, which may contribute to progress of SSc [32, 35, 36].

Asbestos

Asbestos is composed of mineral fibers, i.e., (1) serpentine (chrysotile) and (2) amphibole (actinolite, amosite, anthophyllite, crocidolite, tremolite) [37]. Asbestos is used due to heat resistance, occurring in mining and construction [37].

Previous series have shown that subjects exposed to amphibole more often developed high levels of antinuclear antibodies than non-exposed controls [37, 38]. Noonan et al. [39] have, in fact, found that workers in an asbestos-contaminated vermiculite mining company were at twice the risk of either rheumatoid arthritis, systemic lupus erythematosus, or SSc compared with the unexposed population. Nevertheless, in this group of exposed patients, because asbestos was concurrent with crystalline silica exposure (contaminated vermiculite), it is difficult to assess the role of each material separately. Moreover, based on examination of US death certificates of SSc patients (n=5642), Gold et al. [40] have also observed an

association between occupational asbestos exposure and SSc (OR 1.2, 95 % CI 1.1–1.3).

In experimental models, which are C57BL/6 mice and rats, intratracheal amphibole asbestos has been shown to induce (1) synthesis of antinuclear antibodies [41–43] and (2) modifications of serum cytokine profile, such as marked increase in the concentration of serum IL-17. This Th17 response was characterized by high levels of IL-17 triggered or maintained by other cytokines (e.g., IL-6, IL-23, TGF-β) [44]. Interestingly, Th17 responses have been implicated in the pathogenesis of SSc [45, 46].

Taken together, the limited number of epidemiological series exploring a causal association between asbestos exposure and SSc makes it difficult to draw definite conclusions. Further investigations are therefore warranted to assess the accurate relationship between SSc and occupational exposure to asbestos.

Organic solvents

Organic solvents are compounds that can be dichotomized into aliphatic-chain compounds (*n*-hexane), aromatic compounds (benzene, xylene), and chlorinated compounds. Common uses for organic solvents are for dry cleaning (tetrachloroethylene), paint thinners (toluene), nail polish removers and glue solvents (acetone, methyl acetate, ethyl acetate), and spot removers (hexane) [2]. To date, the applications of organic solvents are increasingly diversified in both developed and developing countries (Table 2).

The association between SSc and organic solvent exposure was first described by Reinl [47]. Previous authors have also evaluated the association between organic solvent exposure and increased risk of SSc [25, 48–51]. In a case–control study (178 patients, 200 controls), Nietert et al. [52] have observed a correlation between solvent exposure and SSc (OR 2, 95 % CI 1.51–2.50). In another case–control series (21 SSc, 42 controls), the association between exposure to organic solvents and SSc was observed only in male patients with SSc [48]. A 2012 meta-analysis included 11 case–control series (1291 cases and 3435 controls), the meta-analytic risk estimate for occupational exposure to organic solvents (ever vs. never) being 2.4 (95 % CI 1.7–3.4) in SSc; the risk of SSc associated with solvent exposure was higher in men (OR 3.0, 95 % CI 1.9–4.6) than in women (OR 1.8, 95 % CI 1.5–2.1) [30]. Furthermore, two series have shown elevated relative risk estimate for high cumulative exposure scores [25, 52]. To date, only few studies have evaluated the association between specific organic solvents and SSc [25, 48, 49, 51, 52]. Some series have reported elevated risks associated with such specific organic solvents—which are trichloroethylene, chlorinated solvents, aromatic solvents, toluene, xylene, and white spirit—with various results [25, 49, 52]. Nietert et al. [52] have observed a correlation between trichloroethylene exposure and SSc (OR 4.4, 95 % CI 1.3–15); by contrast, Garabrant et al. [49] failed to find a significant association between trichloroethylene exposure and SSc (OR 2.29, 95 % CI 0.95–5.71). In a meta-analysis of three series, the risk estimates for occupational trichloroethylene exposure were 2.5 (95 % CI 1.1–5.4) for men and 1.2 (95 % CI 0.6–2.6) for women [53]. In another case–control series (80 patients, 160 controls), a significant association was observed between SSc and aromatic solvents (OR 2.67, 95 % CI 1.06–6.75), chlorinated solvents (OR 2.61, 95 % CI 1.20–5.66), trichloroethylene (OR 2.39, 95 % CI 1.04–5.22), toluene (OR 3.44, 95 % CI 1.09–10.90), white spirit (OR 3.46, 95 % CI 1.48–8.11), ketones (OR 8.78, 95 % CI 1.82–42.38), and any type of solvent (OR 2.66, 95 % CI 1.35–5.23) [25].

Table 2 Occupations associated with exposure to organic solvents

- Sources of exposure to chlorinated solvents
  - Manufacture of raw/refined oils
  - Plastic processing and manufacture of plastics/synthetic rubber
  - Manufacture of artificial/synthetic fibers
  - Manufacture/retreading of tires
  - Manufacture of essential oils
  - Construction of civil ships/pleasure and naval repair
  - Construction of cells of aircraft
  - Manufacture of motor vehicles
  - Manufacture of electronic components
  - Manufacture of adhesives/gelatines
  - Manufacture of paintings/varnishes
  - Work of coatings of the grounds/walls
  - Repair work in clock industry
  - Work of treatments and coatings of metals
  - Work of manufacture and repair of shoes and leather articles
  - Work of printing works
  - Manufacture of laundry and dyeing of large ones/details
- Sources of exposure to aromatic solvents
  - Petrochemical industry
  - Preparation, transfer, and handling of the fuels and workout of cisterns
  - Cleaning, clearing out, and pumping of muds of sumps in the water treatment of refineries
  - Work of production, extraction, and correction of benzene/toluene/xylene in organosynthesis
  - Manufacture and use of varnish, paintings, enamels, cements, inks, adhesives, and products containing toluene and xylene
  - Production and use of dissolutions of natural rubber or synthetic or reviving solvents
  - Manufacture of imitation leather
  - Metallurgy and work of metal industry of papers/paperboards and edition printing works
  - Repair of motor vehicles
- Sources of exposure to ketones
  - Manufacture or use of paintings, varnishes, enamels, cements, adhesives, dyes, and dyeings—printing works

Additionally, a larger case–control study also showed the marked association between SSc and organic solvents for white spirit (OR 7.69, 95 % CI 4.11–14.7), aromatic solvents (OR 8.17, 95 % CI 2.29–36.5), chlorinated solvents (OR 2.46, 95 % CI 1.12–5.32), trichloroethylene (OR 2.26, 95 % CI 0.95–5.26), and ketones (OR 3.37, 95 % CI 1.51–7.53) [2]. However, in this series, exposure to other specific organic solvents was different in both male and female patients [2]. In male patients with SSc, the authors found increased ORs for white spirit (OR 10.29, 95 % CI 3.10–38.90), chlorinated solvents (OR 4.01, 95 % CI 1.2–13.37), and trichloroethylene (OR 2.77, 95 % CI 0.80–9.35); there was also an elevated risk associated with a high final cumulative score (>1) in male patients with SSc compared with male controls for white spirit (OR 5.59, 95 % CI 1.54–21.44), chlorinated solvents (OR 14.09, 95 % CI 2.38–152.20), trichloroethylene (OR 4.49, 95 % CI 1.11–18.89), and ketones (OR 5.92, 95 % CI 1.03–41.95) [2]. Furthermore, in female patients, the authors found increased ORs for white spirit (OR 9.77, 95 % CI 4.06–25.51), aromatic solvents (OR 26.4, 95 % CI 3.45–1183), and ketones (OR 5.52, 95 % CI 1.76–19.37); there was an elevated risk associated with a higher final cumulative score (>1) in female patients with SSc compared with female controls for white spirit (OR 6.22, 95 % CI 2.02–21.28), aromatic solvents (P=0.0008), any type of solvent (OR 4.95, 95 % CI 1.15–17.52), and ketones (OR 7.91, 95 % CI 1.26–84.93) [2]. These authors reported that (1) building trade and painting were more commonly found in patients exposed to white spirit; (2) exposure to aromatic solvents was principally observed in patients in chemistry-related occupations and in workers exposed to petrol; and (3) exposure to chlorinated solvents and trichloroethylene was found in patients working in metal industry and automotive industry and in sheet metal workers, paint/varnish/adhesive manufacturing, and manufacture of electronic components [2]. Altogether, the differences between the occupational exposure to specific organic solvents of male and female SSc patients were explained, in part, by the differences in occupations.

In addition, occupational exposure to organic solvents has been found to be a predictive parameter of SSc severity [4]. Recently, SSc patients who were exposed to organic solvents, compared to non-exposed patients, have been found to exhibit more frequently (i) diffuse cutaneous SSc (P=0.001); (ii) severe microangiopathy as shown by higher prevalence of digital ulcers (P=0.01) and lower median value of left ventricular ejection fraction (P=0.04); (iii) ILD (P=0.02), which was more severe in exposed patients with lower median values of FVC (P=0.005), VC (P=0.002), and DLCO (P=0.02) on pulmonary function tests; (iv) cancer (P=0.003); and (v) positivity of anti-Scl70 antibody (P=0.04) [4]. Interestingly, in this latter series, the authors have found that patients who were exposed to chlorinated solvents, compared to those exposed to white spirit, aromatic solvents, or ketones, had higher median values of Rodnan score (P=0.037) and lower median values of left ventricular ejection fraction (P=0.04), VC (P=0.04), FVC (P=0.03), and DLCO (P=0.009) [4].

The pathogenic mechanisms of organic solvents remain unclear in the onset of SSc. Previous authors have speculated that organic solvents may link with nucleic acids and proteins, resulting in immune disruptors and increased risk of SSc [30]. MRL+/+ mice, when exposed to trichloroethylene, develop higher levels of overall serum IgG and increased prevalence of antinuclear antibodies [54]. Other experimental models have shown that exposure to trichloroethylene led to (1) protein modifications [55–59]; (2) synthesis of higher levels of IL-17 and IL-21 by splenocytes in trichloroethylene-treated mice [60]; (3) production of reactive oxygen species and increased nitric oxide by nitric oxide synthase in cultured human epidermal keratinocytes [61]; (4) Th1 T cell activation in MRL+/+ mice [62]; (5) inhibition of cellular apoptosis of naïve CD4+ and CD8+ T cells in MRL+/+ mice [63]; and (6) DNA hypermethylation on rat cardiac myoblasts [64]. Furthermore, other experimental studies have shown that exposure to benzene resulted in (1) decreased T cell population in wild/captive American kestrel birds [65]; (2) reduced number of CD4+/CD8+ T cells and B cells in exposed workers [66]; (3) increased reactive oxygen species and induction of DNA fragmentation in pump workers [67]; and (4) changes in gene transcription involved in apoptosis, oxidative stress, cellular cycle, and cytokine production in benzene-treated mice [68].

Other industrial chemicals

The association between SSc and other industrial agents related to occupational exposure has more uncommonly been described.

Previous investigators have reported a 2.5-fold higher risk of SSc associated with vinyl chloride, epoxy resins, and/or formaldehyde (OR 2.5, 95 % CI 0.8–8) that was statistically significant in men (OR 18.6, 95 % CI 1.4–251) [24]. In a case–control study (56 SSc patients), the authors failed to find a relationship between epoxy resin exposure and SSc [23]. In another series (80 SSc patients, 160 controls), significantly increased OR for SSc was observed for epoxy resins (OR 4.24, 95 % CI 1.03–17.44) [6]. However, Silman et al. [15] failed to find an association between SSc and epoxy resin exposure (OR 1.7, 95 % CI 0.4–7.3). More recently, in a larger study (100 SSc patients, 300 controls), there was no significant difference between epoxy resin exposure and SSc (OR 3.03, CI 95 % 0.02 to 12.6) [2].

Additionally, one case–control series (80 patients, 160 controls) has shown significant increased OR in SSc for welding fumes (OR 3.74, 95 % CI 1.06–13.18); the risk associated with high cumulative exposure (>1) was increased in SSc (OR 6.41, 95 % CI 1.26–32.49) [25]. Another larger case–

control study (100 SSc patients, 300 controls) demonstrated a significant association between SSc and occupational exposure to welding fumes (OR 2.60, 95 % CI 1.15 to 5.81) [2]. This latter study has shown that the risk of SSc was increased in patients with a high cumulative score (>1) (OR 4.70, 95 % CI 1.09–23.14) for welding fumes [2]. Additionally, there was also an elevated risk in male patients with SSc compared with male controls (OR 8.62, 95 % CI 2.64–32.04) [2]. SSc patients exposed to welding fumes were welders, boilermakers, and electromechanical workers [2].

Finally, there has been no epidemiologic research on risks of SSc associated with relatively widespread metals and synthetic chemical exposures such as plasticizers, phthalates, and bisphenol A.

Pesticides and persistent organic pollutants

Few authors have mentioned that pesticides may contribute to increased risk of rheumatoid arthritis and systemic lupus erythematosus [69, 70]. A recent case–control study (100 SSc patients, 300 controls) failed to find an association between SSc and occupational exposure to pesticides (OR 3.06, 95 % CI 0.04 to 241.94); these latter data may be explained, in part, by the fact that SSc patients and controls included few agricultural workers/farmers (2 vs. 1 %) [2]. Further investigations are thus required to assess accurately the risk of SSc associated with specific pesticide agents.

Furthermore, based on published data, there are also insufficient results showing that exposure to persistent halogenated organic pollutants that are resistant to environmental degradation plays a role in the onset of SSc, including organochlorine pesticides, polychlorinated biphenyls, dioxins, and furans.

Air pollutants

Particulate emission from diesel exhaust engines has been associated with fibrosis [71, 72]. Diesel exhaust nanoparticles have been shown to be internalized by monocyte-derived macrophages and keratinocytes from healthy subjects, leading to oxidative, pro-fibrotic, and pro-inflammatory processes in normal human skin [71, 72]. A recent series has demonstrated that diesel exhaust nanoparticles induced, in vitro, (1) higher mRNA gene expression of metalloproteases 2, 7, 9, and 12; collagen I and III; and vascular endothelial growth factor (VEGF) in SSc fibroblasts than in controls and (2) activation of keratinocytes of patients with diffuse cutaneous SSc with increase of pro-fibrotic cytokines: IL-1α, IL-8, and IL-6 mRNA levels [73]. IL-1α has been reported to be greatly increased in SSc epidermis, and it is speculated to initiate keratinocyte–fibroblast interactions, leading to fibroblast activation [74].

These results suggest that traffic-derived pollution may play a role in SSc genesis. However, no definite conclusion can be drawn from these data, and further investigations are warranted to confirm these preliminary results.

Smoking and drug abuse

Smoking does not confer a risk for SSc onset. In a case–control study (621 SSc, 1228 controls), the authors failed to find an association between SSc and smoking status dichotomized into (1) ever smoking (43 vs. 42.5 %) and (2) never smoking (57 vs. 57.5 %) [75]. However, it is established that cigarette smoking results in significant negative effects on vascular and pulmonary outcomes in SSc [76, 77]. Furthermore, in 606 SSc patients, a correlation has been observed between cigarette smoking and a higher modified Rodnan skin score (P= 0.0029) [78].

Furthermore, cocaine is a vasoconstrictive agent that has also been reported to be associated with SSc-like syndromes [79–82].

Personal care

Silicone

Silicone is one of the major constituents of the Earth's crust and an important trace mineral in bone formation and mineralization [83]. In fact, the silicones used in medical products are heterogeneous in polymer length, side-chain substitutions, and fillers, leading to a great variation in the biological and physical properties of these chemicals [84]. The synthetic polymer may be formed into a gel by lengthening of polymer chains or can be modified into a rubber-like material (elastomer, by cross-linking the polymer chains) [84].

Case reports of women with silicone breast implants who developed SSc were published. Several case–control series and prospective studies of connective tissue diseases (including SSc) and breast implants failed to find an increased risk of SSc associated with breast implants. A meta-analysis (9 cohort studies, 9 case–control studies, and 2 cross-sectional studies) found no association between silicone breast implants and SSc (OR 1.01, 95 % CI 0.59–1.72) [85]. In a 2014 case–control study, the authors did not find any significant difference between SSc patients (n=100) and controls (n=300) regarding previous history of cosmetic surgery using silicone breast implants [2].

Prosthesis

In a 2014 case–control study, the authors did not find any significant difference between SSc patients (n=100) and age- and sex-matched controls (n=300) regarding previous history of prosthesis (OR 0.83, 95 % CI 0.29–2.05) as well as contact lenses (OR 0.74, 95 % CI 0.13–2.83) [2].

Hair dye

In a case–control study, the authors did not find any significant difference between SSc patients (n=100) and age- and sex-matched controls (n=300) regarding previous history of hair dye (OR 0.94, 95 % CI 0.57–1.58) [2].

Drugs

Case reports have identified clusters of SSc in patients receiving therapy, i.e.,

- Antimitotics: bleomycin, taxanes, gemcitabin, tegafur-uracile, interferon α, and aldesleukine [54, 81, 86–92]. Moreover, SSc deterioration related to cisplatin and bleomycin therapy has been reported [90]. Taxane-associated SSc may induce increased synthesis of IL-4 and IL-6 and growth factors, leading to fibroblast activation [86].
- Anorexigens, including diethylpropion chlorhydrate, mazindol, dexamphetamine-metaqualone, fenproporex, and fenfluramine [79, 80, 88, 93–95].
- Tryptophan [88, 96–98].

In a 2014 case–control study, the authors did not find any significant difference between SSc patients (n=100) and age- and sex-matched controls (n=300) regarding the use of the following drugs: anorexigens (OR 1.39, 95 % CI 0.54–3.37), pentazocine (P=0.441), bromocriptine (OR 0.94, 95 % CI 0.22–3.12), and taxanes (OR 3.01, 95 % CI 0.04–237.39) [2].

Skouby et al. [99] have also reported a case of scleroderma-like picture following a single serum injection during vaccination.

Thus, based on our data and literature review, there is insufficient evidence to show that personal care (silicone, prosthesis, hair dye, drugs) exposure plays a causative role in the development of SSc.

Physical agents

Physical agents include ionizing radiation, ultraviolet radiation, and electric and magnetic fields. To date, there is growing evidence for (1) an association between ionizing radiation and risk of autoimmune thyroiditis and Graves' disease and (2) an inverse relationship between ultraviolet exposure and risk of multiple sclerosis [30]. However, no investigators have yet assessed the risk of SSc in patients exposed to physical agents, including ionizing radiation, ultraviolet radiation, and electric and magnetic fields.

Based on current published data, there is thus insufficient evidence that exposure to ionizing radiation, ultraviolet radiation, and electric and magnetic fields is a causative factor of SSc.

Biological agents

Biological agents can be divided into infections and diet, foods, and dietary contaminants.

Infections

Infections have been incriminated to play a role in the SSc pathogenesis. Several mechanisms of infections have been suggested, including endothelial cell damage, molecular mimicry, and self-reactive antibodies [100].

- *Parvovirus B19*: Parvovirus B19 has been speculated as a causative agent in SSc because (1) serum parvovirus B19 viremia has been more often detected in SSc patients than in healthy subjects (4 vs. 0.6 %) [101, 102] and (2) the presence of the parvovirus B19 has been detected in bone marrow biopsy specimens of 57 % of SSc patients [103], suggesting that the bone marrow may represent a reservoir from which the parvovirus B19 virus spreads to SSc tissues [104]. Endothelial injury in patients with parvovirus B19 has been suggested to reflect a combination of direct viral cytotoxicity and humoral immunity [105]. It has also been found that parvovirus B19 exerts a cytotoxic effect on infected cells through a non-structural protein NS-1 [106]. The ability of parvovirus B19 to persistently infect SSc fibroblasts might be responsible for marked cell alterations [107].
- *Cytomegalovirus*: Cytomegalovirus may play a role in SSc onset due to its ability to infect both endothelial and monocyte/macrophage cells and through the upregulation of fibrogenic cytokines and induction of immune dysregulation [108, 109]; the onset of SSc shortly after an acute episode of viral infection suggested cytomegalovirus as a possible trigger for SSc. Infection of endothelial cells alters the expression of different integrins and may induce the expression of fibrogenic cytokines and dysregulation of different antibodies, especially anti-Scl70 antibody [108, 110]; anti-Scl70 antibody could cross-react with a peptide sequence of the UL-70 protein of cytomegalovirus [111].
- *Helicobacter pylori*: Previous authors have reported increased prevalence of *H. pylori* in SSc patients, compared with healthy subjects [112–114]. In 42 SSc patients, *H. pylori* infection has also been found to be associated with SSc activity, especially with higher values of Rodnan score (P<0.0001) [115]. It has been speculated that *H. pylori* sheds extracellular products and notably heat shock protein 60 (HSP 60) eliciting local and systemic immune responses and leading subsequently to tissue damage [116]. However, there are other conflicting and controversial data regarding the association of *H. pylori* infection with SSc.

Altogether, based on current published data, there is insufficient evidence to show that infections play a causative role in the development of SSc.

Diet, foods, and dietary contaminants

Regarding dietary factors in autoimmune diseases, the gold standard is the causation of celiac disease by gluten ingestion [30]. Furthermore, there is evidence for association between outbreaks of (1) toxic oil syndrome and ingestion of contaminated rapeseed oil containing 1,2-di-oleyl ester and oleic anilide [117–119] and (2) eosinophilia–myalgia syndrome and L-tryptophan supplements [96, 98, 120].

Nutritional sources may provide the methyl donors and cofactors (folic acid, vitamin B_{12}, and pyridoxal phosphate) essential for DNA and histone methylation. There are reports of diet-induced epigenetic changes in the adult state [121]. It has been proposed that epigenetic links between nutrition and autoimmunity may contribute to several autoimmune diseases.

However, to date, based on current published data, there is insufficient evidence to show that diet, foods, and dietary contaminants play a causative role in the development of SSc, including (1) breast-feeding and the age at which certain foods are introduced into an infant's diet; (2) exposure to complex foods early in infancy; (3) low antioxidant vitamin intake, low fruit or fiber intake, and high sweets or fat intake; (4) low alcohol consumption; and (5) consumption of food chemicals, dyes or additives, as well as nitrates, nitrites, nitrosamines.

Conclusion

As a mirror image of the Roman god Janus Bifrons, the environment has a hidden face. To highlight this hidden face of the environment in the field of autoimmune diseases and particularly in SSc will allow to see responsible agents emerging in the very near future. To date, there is, in fact, a growing scientific evidence that environmental factors have a crucial impact on both alterations and modulation of epigenetic determinants, resulting in SSc onset and progression. Interestingly, a marked correlation has been found between SSc onset and occupational exposure to crystalline silica and the following organic solvents: white spirit, aromatic solvents, chlorinated solvents, trichloroethylene, and ketones; the risk associated with high cumulative exposure to silica and organic solvents further appears to be strongly increased in SSc. Altogether, occupational exposure should be systematically checked in all SSc patients at diagnosis, as (1) exposed patients seem to develop more severe forms of SSc, especially diffuse cutaneous SSc, severe microangiopathy, and ILD, and (2) the identification of the occupational toxic agent will allow its interruption, which may lead to potential improvement of SSc outcome [2, 4, 121]. Therefore, further investigations are still warranted to identify other environmental factors that may be associated with SSc onset and progression.

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Conflict of interest The authors declare that they have no competing interests.

References

1. Marie I, Antonietti M, Houivet E, Hachulla E, Maunoury V, Bienvenu B, Viennot S, Smail A, Duhaut P, Dupas JL, Dominique S, Hatron PY, Levesque H, Benichou J, Ducrotté P (2014) Gastrointestinal mucosal abnormalities using videocapsule endoscopy in systemic sclerosis. Aliment Pharmacol Ther 40: 189–199
2. Marie I, Gehanno JF, Bubenheim M, Duval-Modeste AB, Joly P, Dominique S, Bravard P, Noël D, Cailleux AF, Weber J, Lagoutte P, Benichou J, Levesque H (2014) Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. Autoimmun Rev 13:151–156
3. Marie I, Leroi AM, Menard JF, Levesque H, Quillard M, Ducrotte P (2015) Fecal calprotectin in systemic sclerosis and review of the literature. Autoimmun Rev 14:547–554
4. Marie I, Menard JF, Duval-Modeste AB, Joly P, Dominique S, Bravard P, Noël D, Gehanno JF, Bubenheim M, Benichou J, Levesque H (2015) Association of occupational exposure with features of systemic sclerosis. J Am Acad Dermatol 72:456–464
5. Altorok N, Almeshal N, Wang Y, Kahaleh B (2014) Epigenetics, the holy grail in the pathogenesis of systemic sclerosis. Rheumatology (Oxford) Apr 16
6. Ciechomska M, van Laar J, O'Reilly S (2015) Current frontiers in systemic sclerosis pathogenesis. Exp Dermatol. doi:10.1111/exd.12673
7. Marie I, Bény JL (2002) Endothelial dysfunction in murine model of systemic sclerosis: tight-skin mice 1. J Invest Dermatol 119: 1379–87
8. van Bon L, Affandi AJ, Broen J, Christmann RB, Marijnissen RJ, Stawski L, Farina GA, Stifano G, Mathes AL, Cossu M, York M, Collins C, Wenink M, Huijbens R, Hesselstrand R, Saxne T, DiMarzio M, Wuttge D, Agarwal SK, Reveille JD, Assassi S, Mayes M, Deng Y, Drenth JP, de Graaf J, den Heijer M, Kallenberg CG, Bijl M, Loof A, van den Berg WB, Joosten LA, Smith V, de Keyser F, Scorza R, Lunardi C, van Riel PL, Vonk M, van Heerde W, Meller S, Homey B, Beretta L, Roest M, Trojanowska M, Lafyatis R, Radstake TR (2014) Proteome-wide analysis and CXCL4 as a biomarker in systemic sclerosis. N Engl J Med 370:433–443
9. Ciechomska M, van Laar JM, O'Reilly S (2014) Emerging role of epigenetics in systemic sclerosis pathogenesis. Genes Immun 15: 433–439
10. Luo Y, Wang Y, Wang Q, Xiao R, Lu Q (2013) Systemic sclerosis: genetics and epigenetics. J Autoimmun 41:161–167
11. Lu Q (2013) The critical importance of epigenetics in autoimmunity. J Autoimmun 41:1–5
12. Lei W, Luo Y, Lei W, Luo Y, Yan K, Zhao S, Li Y, Qiu X, Zhou Y, Long H, Zhao M, Liang Y, Su Y, Lu Q (2009) Abnormal DNA methylation in CD4+ T cells from patients with systemic lupus erythematosus, systemic sclerosis, and dermatomyositis. Scand J Rheumatol 38:369–374

13. Lian X, Xiao R, Hu X, Kanekura T, Jiang H, Li Y, Wang Y, Yang Y, Zhao M, Lu Q (2012) DNA demethylation of CD40l in CD4+ T cells from women with systemic sclerosis: a possible explanation for female susceptibility. Arthritis Rheum 64:2338–2345
14. Wang Y, Kahaleh B (2013) Epigenetic repression of bone morphogenetic protein receptor II expression in scleroderma. J Cell Mol Med 17:1291–1299
15. Ghosh AK, Bhattacharyya S, Lafyatis R, Farina G, Yu J, Thimmapaya B, Wei J, Varga J (2013) p300 is elevated in systemic sclerosis and its expression is positively regulated by TGF-β: epigenetic feed-forward amplification of fibrosis. J Invest Dermatol 133:1302–1310
16. Wei J, Ghosh AK, Chu H, Fang F, Hinchcliff ME, Wang J, Marangoni RG, Varga J (2015) The histone deacetylase sirtuin 1 is reduced in systemic sclerosis and abrogates fibrotic responses by targeting transforming growth factor β signaling. Arthritis Rheumatol 67:1323–1334
17. O'Reilly S, Hügle T, van Laar JM (2012) T cells in systemic sclerosis: a reappraisal. Rheumatology (Oxford) 51:1540–1549
18. Selmi C, Leung PS, Sherr DH, Diaz M, Nyland JF, Monestier M, Rose NR, Gershwin ME (2012) Mechanisms of environmental influence on human autoimmunity: a National Institute of Environmental Health Sciences expert panel workshop. J Autoimmun 39:272–284
19. Takemoto R, Jinnin M, Wang Z, Kudo H, Inoue K, Nakayama W, Ichihara A, Igata T, Kajihara I, Fukushima S, Ihn H (2013) Hair miR-29a levels are decreased in patients with scleroderma. Exp Dermatol 22:832–833
20. Nakashima T, Jinnin M, Yamane K, Honda N, Kajihara I, Makino T, Masuguchi S, Fukushima S, Okamoto Y, Hasegawa M, Fujimoto M, Ihn H (2012) Impaired IL-17 signaling pathway contributes to the increased collagen expression in scleroderma fibroblasts. J Immunol 188:3573–3583
21. Jüngel A, Distler JH, Gay S, Distler O (2011) Epigenetic modifications: novel therapeutic strategies for systemic sclerosis? Expert Rev Clin Immunol 7:475–480
22. Bramwell B (1914) Diffuse scleroderma: its frequency and occurrence in stonemasons; its treatment by fibrinolysin: elevations of temperature due to fibrinolysin injections. Edinburg Med J 12:387
23. Erasmus LD (1957) Scleroderma in goldminers on the Witwatersrand with particular reference to pulmonary manifestations. S Afr Lab Clin Med 3:209–231
24. Calvert GM, Rice FL, Boiano JM, Sheehy JW, Sanderson WT (2003) Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. Occup Environ Med 60:122–129
25. Diot E, Lesire V, Guilmot JL, Metzger MD, Pilore R, Rogier S, Stadler M, Diot P, Lemarie E, Lasfargues G (2002) Systemic sclerosis and occupational risk factors: a case–control study. Occup Environ Med 59:545–549
26. Englert H, O'connor H, Small-McMahon J, Chambers P, Davis K, Brooks P (2000) Male systemic sclerosis and occupational silica exposure—a population based study. Aust N Z J Med 30:215–220
27. Silman AJ, Jones S (1992) What is the contribution of occupational environmental factors to the occurrence of scleroderma in men? Ann Rheum Dis 51:1322–1324
28. Sluis-Cremer GK, Hassel PA, Nizdo EH, Churchill AR, Zeiss EA (1985) Silica, silicosis and progressive systemic sclerosis. Br J Ind Med 41:838–843
29. Haustein UF, Ziegler V, Hermann K, Mehlhorn J, Schmidt C (1990) Silica-induced scleroderma. J Am Acad Dermatol 22: 444–448
30. Miller FW, Alfredsson L, Costenbader KH, Kamen DL, Nelson LM, Norris JM, De Roos AJ (2012) Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. J Autoimmun 39:259–271
31. Moisan S, Rucay P, Ghali A, Penneau-Fontbonne D, Lavigne C (2010) Silica-associated limited systemic sclerosis after occupational exposure to calcined diatomaceous earth. Joint Bone Spine 77:472–473
32. Maeda M, Nishimura Y, Kumagai N, Hayashi H, Hatayama T, Katoh M, Miyahara N, Yamamoto S, Hirastuka J, Otsuki T (2010) Dysregulation of the immune system caused by silica and asbestos. J Immunotoxicol 7:268–278
33. Otsuki T, Maeda M, Murakami S, Hayashi H, Miura Y, Kusaka M, Nakano T, Fukuoka K, Kishimoto T, Hyodoh F, Ueki A, Nishimura Y (2007) Immunological effects of silica and asbestos. Cell Mol Immunol 4:261–268
34. Lee S, Hayashi H, Maeda M, Chen Y, Matsuzaki H, Takei-Kumagai N, Nishimura Y, Fujimoto W, Otsuki T (2012) Environmental factors producing autoimmune dysregulation—chronic activation of T cells caused by silica exposure. Immunobiology 217:743–748
35. Otsuki T, Hayashi H, Nishimura Y, Hyodo F, Maeda M, Kumagai N, Miura Y, Kusaka M, Uragami K (2011) Dysregulation of autoimmunity caused by silica exposure and alteration of Fas-mediated apoptosis in T lymphocytes derived from silicosis patients. Int J Immunopathol Pharmacol 24:11S–16S
36. Pfau JC, Serve KM, Noonan CW (2014) Autoimmunity and asbestos exposure. Autoimmune Dis 2014:782045
37. Nigam SK, Suthar AM, Patel MM, Karnik AB, Dave SK, Kashyap SK, Venkaiah K (1993) Humoral immunological profile of workers exposed to asbestos in asbestos mines. Indian J Med Res 98:274–277
38. Noonan CW, Pfau JC, Larson TC, Spence MR (2006) Nested case–control study of autoimmune disease in an asbestos-exposed population. Environ Health Perspect 114:1243–1247
39. Gold LS, Ward MH, Dosemeci M, De Roos AJ (2007) Systemic autoimmune disease mortality and occupational exposures. Arthritis Rheum 56:3189–3201
40. Ferro A, Zebedeo CN, Davis C, Ng KW, Pfau JC (2014) Amphibole, but not chrysotile, asbestos induces anti-nuclear autoantibodies and IL-17 in C57BL/6 mice. J Immunotoxicol 11: 283–290
41. Salazar KD, Copeland CB, Wood CE, Schmid JE, Luebke RW (2013) Evaluation of anti-nuclear antibodies and kidney pathology in Lewis rats following exposure to Libby amphibole asbestos. J Immunotoxicol 10:329–333
42. Salazar KD, Copeland CB, Luebke RW (2012) Effects of Libby amphibole asbestos exposure on two models of arthritis in the Lewis rat. J Toxicol Environ Health 75:351–365
43. Furuzawa-Carballeda J, Vargas-Rojas MI, Cabral AR (2007) Autoimmune inflammation from the Th17 perspective. Autoimmun Rev 6:169–175
44. Afzali B, Lombardi G, Lechler RI, Lord GM (2007) The role of T helper 17 (Th17) and regulatory T cells (Treg) in human organ transplantation and autoimmune disease. Clin Exp Immunol 148: 32–346
45. Rodríguez-Reyna TS, Furuzawa-Carballeda J, Cabiedes J, Fajardo-Hermosillo LD, Martínez-Reyes C, Díaz-Zamudio M, Llorente L (2012) Th17 peripheral cells are increased in diffuse cutaneous systemic sclerosis compared with limited illness: a cross-sectional study. Rheumatol Int 32:2653–2660
46. Reinl W (1957) Sklerodermie durch trichloräthylen-einwirkung? Zent F Arbeitsmd u Arbettsschutz 7:58–60
47. Bovenzi M, Barbone F, Pisa FE, Betta A, Romeo L, Tonello A, Biasi D, Caramaschi P (2004) A case–control study of occupational exposures and systemic sclerosis. Int Arch Occup Environ Health 77:10–16

48. Garabrant DH, Lacey JV Jr, Laing TJ, Gillepsie BW, Mayes MD, Cooper BC (2003) Scleroderma and solvent exposure among women. Am J Epidemiol 157:493–500
49. Kettaneh A, Al Moufti O, Tiev KP, Chayet C, Toledano C, Fabre B, Fardet L, Cabane J (2007) Occupational exposure to solvents and gender-related risk of systemic sclerosis: a metaanalysis of case–control studies. J Rheumatol 34:97–103
50. Maître A, Hours M, Bonneterre V, Arnaud J, Tülin-Arslan M, Carpentier P, Bergeret A, de Gaudemaris R (2004) Systemic sclerosis and occupational risk factors: role of solvents and cleaning products. J Rheumatol 31:2395–2401
51. Nietert PJ, Sutherland SE, Silver RM, Pandey JP, Knapp RG, Hoel DG, Dosemeci M (1998) Is occupational organic solvent exposure a risk factor for scleroderma? Arthritis Rheum 41:1111–1118
52. Cooper GS, Makris SL, Nietert PJ, Jinot J (2009) Evidence of autoimmune-related effects of trichloroethylene exposure from studies in mice and humans. Environ Health Perspect 117:696–702
53. Khan MF, Kaphalia BS, Prabhakar BS, Kanz MF, Ansari GA (1995) Trichloroethene-induced autoimmune response in female MRL +/+ mice. Toxicol Appl Pharmacol 134:155–160
54. Cai P, König R, Khan MF, Kaphalia BS, Ansari GA (2007) Differential immune responses to albumin adducts of reactive intermediates of trichloroethene in MRL+/+ mice. Toxicol Appl Pharmacol 220:278–283
55. Grune T, Michel P, Sitte N, Eggert W, Albrecht-Nebe H, Esterbauer H, Siems WG (1997) Increased levels of 4-hydroxynonenal modified proteins in plasma of children with autoimmune diseases. Free Radic Biol Med 23:357–360
56. Halmes NC, Perkins EJ, McMillan DC, Pumford NR (1997) Detection of trichloroethylene-protein adducts in rat liver and plasma. Toxicol Lett 92:187–194
57. Wang G, Ansari GA, Khan MF (2007) Involvement of lipid peroxidation-derived aldehyde-protein adducts in autoimmunity mediated by trichloroethene. J Toxicol Environ Health 70:1977–1985
58. Wang G, König R, Ansari GA, Khan MF (2008) Lipid peroxidation-derived aldehyde-protein adducts contribute to trichloroethene-mediated autoimmunity via activation of CD4+ T cells. Free Radic Biol Med 44:1475–1482
59. Wang G, Wang J, Fan X, Ansari GA, Khan MF (2012) Protein adducts of malondialdehyde and 4-hydroxynonenal contribute to trichloroethene-mediated autoimmunity via activating Th17 cells: dose- and time-response studies in female MRL+/+ mice. Toxicology 292:113–122
60. Shen T, Zhu QX, Yang S, Ding R, Ma T, Ye LP, Wang LJ, Liang ZZ, Zhang XJ (2007) Trichloroethylene induce nitric oxide production and nitric oxide synthase mRNA expression in cultured normal human epidermal keratinocytes. Toxicology 239:186–194
61. Griffin JM, Blossom SJ, Jackson SK, Gilbert KM, Pumford NR (2000) Trichloroethylene accelerates an autoimmune response by Th1 T cell activation in MRL +/+ mice. Immunopharmacology 46:123–137
62. Blossom SJ, Doss JC (2007) Trichloroethylene alters central and peripheral immune function in autoimmune-prone MRL(+/+) mice following continuous developmental and early life exposure. J Immunotoxicol 4:129–141
63. Palbykin B, Borg J, Caldwell PT, Rowles J, Papoutsis AJ, Romagnolo DF, Selmin OI (2011) Trichloroethylene induces methylation of the Serca2 promoter in H9c2 cells and embryonic heart. Cardiovasc Toxicol 11:204–214
64. Olsgard ML, Bortolotti GR, Trask BR, Smits JE (2008) Effects of inhalation exposure to a binary mixture of benzene and toluene on vitamin a status and humoral and cell-mediated immunity in wild and captive American kestrels. J Toxicol Environ Health 71:1100–1108
65. Lan Q, Zhang L, Li G, Vermeulen R, Weinberg RS, Dosemeci M, Rappaport SM, Shen M, Alter BP, Wu Y, Kopp W, Waidyanatha S, Rabkin C, Guo W, Chanock S, Hayes RB, Linet M, Kim S, Yin S, Rothman N, Smith MT (2004) Hematotoxicity in workers exposed to low levels of benzene. Science 306:1774–1776
66. Emara AM, El-Bahrawy H (2008) Green tea attenuates benzene-induced oxidative stress in pump workers. J Immunotoxicol 5:69–80
67. Park HJ, Oh JH, Yoon S, Rana SV (2008) Time dependent gene expression changes in the liver of mice treated with benzene. Biomark Insights 3:191–201
68. Cooper GS, Parks CG, Treadwell EL, St Clair EW, Gilkeson GS, Dooley MA (2004) Occupational risk factors for the development of systemic lupus erythematosus. J Rheumatol 31:1928–1933
69. De Roos AJ, Cooper GS, Alavanja MC, Sandler DP (2005) Rheumatoid arthritis among women in the agricultural health study: risk associated with farming activities and exposures. Ann Epidemiol 15:762–770
70. Su DS, Serafino A, Müller JO, Jentoft RE, Schlögl R, Fiorito S (2008) Cytotoxicity and inflammatory potential of soot particles of low-emission diesel engines. Environ Sci Technol 42:1761–1765
71. Fiorito S, Mastrofrancesco A, Cardinali G, Rosato E, Salsano F, Su DS, Serafino A, Picardo M (2011) Effects of carbonaceous nanoparticles from low-emission and older diesel engines on human skin cells. Carbon 49:5038–5048
72. Mastrofrancesco A, Alfè M, Rosato E, Gargiulo V, Beatrice C, Di Blasio G, Zhang B, Su DS, Picardo M, Fiorito S (2014) Proinflammatory effects of diesel exhaust nanoparticles on scleroderma skin cells. J Immunol Res 2014:138751
73. Aden N, Nuttall A, Shiwen X, de Winter P, Leask A, Black CM, Denton CP, Abraham DJ, Stratton RJ (2010) Epithelial cells promote fibroblast activation via IL-1alpha in systemic sclerosis. J Invest Dermatol 130:2191–2200
74. Chaudhary P, Chen X, Assassi S, Gorlova O, Draeger H, Harper BE, Gonzalez E, McNearney T, Perry M, Arnett FC, Mayes MD (2011) Cigarette smoking is not a risk factor for systemic sclerosis. Arthritis Rheum 63:3098–3102
75. Hissaria P, Roberts-Thomson PJ, Lester S, Ahern MJ, Smith MD, Walker JG (2011) Cigarette smoking in patients with systemic sclerosis reduces overall survival: comment on the article by Hudson et al. Arthritis Rheum 63:1758–1759
76. Hudson M, Lo E, Baron M, Steele R, Canadian Scleroderma Research Group (2011) Modeling smoking in systemic sclerosis: a comparison of different statistical approaches. Arthritis Care Res (Hoboken) 63:570–578
77. Gyger G, Hudson M, Lo E, Steele R, Canadian Scleroderma Research Group (CSRG), Baron M (2013) Does cigarette smoking mitigate the severity of skin disease in systemic sclerosis? Rheumatol Int 33:943–948
78. D'Cruz D (2000) Autoimmune diseases associated with drugs, chemicals and environmental factors. Toxicol Lett 112–113:421–32
79. Haustein UF (2005) Scleroderma and pseudo-scleroderma: uncommon presentations. Clin Dermatol 23:480–490
80. Jablonska S, Blaszczyk M (1998) Scleroderma-like disorders. Semin Cutan Med Surg 17:65–76
81. Vergne P, Bertin P, Bonnet C, Scotto C, Trèves R (2000) Drug-induced rheumatic disorders: incidence, prevention and management. Drug Saf 23:279–293
82. Lidar M, Agmon-Levin N, Langevitz P, Shoenfeld Y (2012) Silicone and scleroderma revisited. Lupus 21:121–127
83. Bridges AJ, Vasey FB (1993) Silicone breast implants. History, safety, and potential complications. Arch Intern Med 153:2638–2644

84. Janowsky EC, Kupper LL, Hulka BS (2000) Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med 342:781–790
85. Alexandrescu DT, Bhagwati NS, Wiernik PH (2005) Chemotherapy-induced scleroderma: a pleiomorphic syndrome. Clin Exp Dermatol 30:141–145
86. Beretta L, Caronni M, Vanoli M, Scorza R (2002) Systemic sclerosis after interferon-alfa therapy for myeloproliferative disorders. Br J Dermatol 147:385–386
87. Hallé O, Schaeverbeke T, Bannwarth B, Dehais J (1997) Les facteurs d'environnement et les éléments iatrogènes dans la sclérodermie systémique et les syndromes apparentés. Revue de la littérature. Rev Med Interne 18:219–229
88. Läuchli S, Trüeb RM, Fehr M, Hafner J (2002) Scleroderma-like drug reaction to paclitaxel (Taxol). Br J Dermatol 147:619–621
89. Marie I, Levesque H, Plissonnier D, Balguerie X, Cailleux N, Courtois H (2000) Digital necrosis related to cisplatin in systemic sclerosis. Br J Dermatol 142:833–834
90. Marie I, Joly P, Courville P, Levesqsue H (2007) Pseudosystemic sclerosis as a complication of recombinant human interleukin 2 (aldesleukin) therapy. Br J Dermatol 156:182–183
91. Vial T, Choquet-Kastylevsky G, Descotes J (2002) Adverse effects of immunotherapeutics involving the immune system. Toxicology 174:3–11
92. Bannwarth B (2007) Drug-induced musculoskeletal disorders. Drug Saf 30:27–46
93. Haustein UF, Haupt B (1998) Drug-induced scleroderma and sclerodermiform conditions. Clin Dermatol 16:353–366
94. Pang BK, Munro V, Kossard S (1996) Pseudoscleroderma secondary to phytomenadione (vitamin K1) injections: Texier's disease. Australas J Dermatol 37:44–47
95. Blackburn WD Jr (1997) Eosinophilia myalgia syndrome. Semin Arthritis Rheum 26:788–793
96. Guis S, Mattéi JP, Lioté F (2003) Drug-induced and toxic myopathies. Best Pract Res Clin Rheumatol 17:877–907
97. Hertzman PA, Clauw DJ, Kaufman LD, Varga J, Silver RM, Thacker HL, Mease P, Espinoza LR, Pincus T (1995) The eosinophilia-myalgia syndrome: status of 205 patients and results of treatment 2 years after onset. Ann Intern Med 122:851–855
98. Skouby AP (1949) Sclerodermia-like picture following a single serum injection. Acta Med Scand 136:51–55
99. Grossman C, Dovrish Z, Shoenfeld Y, Amital H (2011) Do infections facilitate the emergence of systemic sclerosis? Autoimmun Rev 10:244–247
100. Ferri C, Longombardo G, Azzi A, Zakrzewska K (1999) Parvovirus B19 and systemic sclerosis. Clin Exp Rheumatol 17: 267–268
101. Yoto Y, Kudoh T, Haseyama K, Suzuki N, Oda T, Katoh T, Takahashi T, Sekiguchi S, Chiba S (1995) Incidence of human parvovirus B19 DNA detection in blood donors. Br J Haematol 91:1017–1018
102. Ferri C, Zakrzewska K, Longombardo G, Giuggioli D, Storino FA, Pasero G, Azzi A (1999) Parvovirus B19 infection of bone marrow in systemic sclerosis patients. Clin Exp Rheumatol 17: 718–720
103. Cassinotti P, Burtonboy G, Fopp M, Siegl G (1997) Evidence for persistence of human parvovirus B19 DNA in bone marrow. J Med Virol 53:229–232
104. Magro CM, Nuovo G, Ferri C, Crowson AN, Giuggioli D, Sebastiani M (2004) Parvoviral infection of endothelial cells and stromal fibroblasts: a possible pathogenetic role in scleroderma. J Cutan Pathol 31:43–50
105. Sol N, Le Junter J, Vassias I, Freyssinier JM, Thomas A, Prigent AF, Rudkin BB, Fichelson S, Morinet F (1999) Possible interactions between the NS-1 protein and tumor necrosis factor alpha pathways in erythroid cell apoptosis induced by human parvovirus B19. J Virol 73:8762–8770
106. Ferri C, Giuggioli D, Sebastiani M, Panfilo S, Abatangelo G, Zakrzewska K, Azzi A (2002) Parvovirus B19 infection of cultured skin fibroblasts from systemic sclerosis patients: comment on the article by Ray et al. Arthritis Rheum 46:2262–2263, **author reply 2263–4**
107. Pandey JP, LeRoy EC (1998) Human cytomegalovirus and the vasculopathies of autoimmune diseases (especially scleroderma), allograft rejection, and coronary restenosis. Arthritis Rheum 41: 10–15
108. Vaughan JH, Shaw PX, Nguyen MD, Medsger TA Jr, Wright TM, Metcalf JS, Leroy EC (2000) Evidence of activation of 2 herpesviruses, Epstein-Barr virus and cytomegalovirus, in systemic sclerosis and normal skins. J Rheumatol 27:821–823
109. Shahgasempour S, Woodroffe SB, Sullivan-Tailyour G, Garnett HM (1997) Alteration in the expression of endothelial cell integrin receptors alpha 5 beta 1 and alpha 2 beta 1 and alpha 6 beta 1 after in vitro infection with a clinical isolate of human cytomegalovirus. Arch Virol 142:125–138
110. Magen E, Delgado JS (2014) Helicobacter pylori and skin autoimmune diseases. World J Gastroenterol 20:1510–1516
111. Danese S, Zoli A, Cremonini F, Gasbarrini A (2000) High prevalence of Helicobacter pylori type I virulent strains in patients with systemic sclerosis. J Rheumatol 27:1568–1569
112. Kalabay L, Fekete B, Czirják L, Horváth L, Daha MR, Veres A, Fónyad G, Horváth A, Viczián A, Singh M, Hoffer I, Füst G, Romics L, Prohászka Z (2002) Helicobacter pylori infection in connective tissue disorders is associated with high levels of antibodies to mycobacterial hsp65 but not to human hsp60. Helicobacter 7:250–256
113. Yazawa N, Fujimoto M, Kikuchi K, Kubo M, Ihn H, Sato S, Tamaki T, Tamaki K (1998) High seroprevalence of Helicobacter pylori infection in patients with systemic sclerosis: association with esophageal involvement. J Rheumatol 25:650–653
114. Radić M, Martinović Kaliterna D, Bonacin D, Morović Vergles J, Radić J (2010) Correlation between Helicobacter pylori infection and systemic sclerosis activity. Rheumatology (Oxford) 49:1784–1785
115. Macchia G, Massone A, Burroni D, Covacci A, Censini S, Rappuoli R (1993) The Hsp60 protein of Helicobacter pylori: structure and immune response in patients with gastroduodenal diseases. Mol Microbiol 9:645–652
116. Alonso-Ruiz A, Calabozo M, Perez-Ruiz F, Mancebo L (1993) Toxic oil syndrome. A long-term follow-up of a cohort of 332 patients. Medicine (Baltimore) 72:285–295
117. Marie I (2008) Connectivites et pseudo-connectivites d'origine médicamenteuse et toxique. In: Rousset H, Vital Durand D, Dupond JL, Pavic M (eds) Diagnostics difficiles en Médecine interne, 3rd edn. Maloine, Paris, pp 179–196
118. Posada de la Paz M, Philen RM, Borda AI (2001) Toxic oil syndrome: the perspective after 20 years. Epidemiol Rev 23:231–247
119. Allen JA, Peterson A, Sufit R, Hinchcliff ME, Mahoney JM, Wood TA, Miller FW, Whitfield ML, Varga J (2011) Post-epidemic eosinophilia-myalgia syndrome associated with L-tryptophan. Arthritis Rheum 63:3633–3639
120. Choi SW, Friso S (2010) Epigenetics: a new bridge between nutrition and health. Adv Nutr 1:8–16
121. Marie I (2014) Sclérodermie systémique et exposition professionnelle : vers une extension de la reconnaissance de maladie professionnelle en 2014 ? Rev Med Interne 35:631–635