# Occupational and Environmental Exposures as Risk Factors for Systemic Lupus Erythematosus

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Although genetic susceptibility plays a strong role in the etiology of systemic lupus erythematosus (SLE), recent research has provided new evidence of the potential influence of environmental factors in the risk for this disease. This paper describes epidemiologic and experimental research pertaining to occupational and environmental sources of exposure to respirable crystalline silica, solvents and pesticides, and two "lifestyle" factors (smoking and hair dye use). As has been seen with other systemic autoimmune diseases (eg, systemic sclerosis and rheumatoid arthritis), a series of epidemiologic studies, using different designs in different settings, have demonstrated relatively strong and consistent associations between occupational silica exposure and SLE. The type and quality of exposure assessment is an important consideration in evaluating these studies. Recent experimental studies examined the effect of trichloroethylene exposure in MRL+/+ mice, but to date there have been few epidemiologic studies of solvents and SLE. There are numerous avenues with respect to environmental factors in SLE that need additional research.

## Introduction

Genetic susceptibility clearly plays a role in the etiology of systemic lupus erythematosus (SLE). In 1975, Block *et al.* [1] estimated that the concordance rate for SLE among monozygotic twins was approximately 60%, based on a compilation of published case reports. However, in two studies published in the 1990s [2,3] the concordance rate was 25% to 35%. The designs of these more recent studies (a national twin-study in the United States and a population-based twin registry study in Finland) are less susceptible to publication bias, suggesting the lower estimates better reflect the true rate in the population. This concordance rate is still much higher than that seen in dizygotic twins (< 5%), and is among the highest rates seen in any autoimmune disease [4•]. However, the relatively low concordance (compared with earlier estimates) provides more support for the idea that other factors, in addition to genetics, are involved in the etiology of SLE.

Environmental (or nongenetic) influences on the development of SLE could include infectious agents and chemical or other compounds that may modulate immune response. "Environment" encompasses occupational exposures, environmental pollutants, and behavioral factors such as smoking and diet. There are many points when environmental exposures may act, including production of autoreactive T cells and of autoantibodies, stimulation of pro- and antiinflammatory cytokines, and target end organ damage. In this paper we discuss environmental agents that have recently been examined with respect to etiology of SLE. This research primarily focuses on occupational exposures (specifically to silica, solvents, and pesticides), smoking, and hair dyes.

## Crystalline Silica

### Epidemiologic studies

Crystalline silica, or quartz (a compound distinctly different from the polymer, silicone), is an abundant mineral found in sand, rock, and soil. High-level exposure to respirable silica dust (particles < 5 μm) can cause chronic inflammation and fibrosis in the lung and other organs. The chronic, progressive lung disease silicosis is a known occupational hazard of the "dusty trades" such as pottery and china manufacturing, quarry work, masonry, and mining [5]. Initial research (dating back to 1914) [6], linking silica dust exposure (or silicosis) to autoimmune diseases, was based on numerous case reports and small case series in specific occupational settings (stone masons and miners) focusing on scleroderma (systemic sclerosis) [7] and rheumatoid arthritis [8].

Since 1985 there have been several developments in the research pertaining to occupational silica exposure and autoimmune diseases. The number of epidemiologic studies, using a variety of study designs (clinic based, occupation-based, population-based, registry-based), conducted in different settings, and involving a spectrum of systemic

diseases (rheumatoid arthritis, primary systemic vasculitis, systemic sclerosis, and SLE) has increased substantially. The literature was reviewed by Parks *et al*. in 1999 [9••] and updated in 2002 [10]. Since then other studies have been published including a meta-analyses of rheumatoid arthritis [11]. This literature is noteworthy in that relatively strong associations with these diseases have been reported (relative risks of 3.0 and higher, with some studies reporting more than a 10-fold increased risk). These associations are similar in magnitude to those seen between cigarette smoking and various kinds of cancer.

Six studies published since 1990 have provided data on occupational silica exposure and SLE (Table 1). These include a case-series that included 87 SLE patients in France [12] and a study of 50 scouring powder factory workers in Spain where three lupus and five lupus/scleroderma overlap cases were found [13]. Conrad *et al*. [14] reported 28 definite and 15 possible SLE cases among 28,000 male uranium miners. This disease prevalence is more than 10 times higher than expected based on sex-specific prevalence rates in the general population. Two other studies examined SLE in silicosis patients using various registries as data sources [15,16]. The larger of these studies was from Sweden. SLE was more frequently diagnosed (risk ratio = 23.8) in patients with silicosis ($n$ = 1052) compared with all other hospitalized patients. Finally, a recent case-control study in the southeastern United States reported a dose-response association with silica dust exposure (odds ratios [OR] = 2 to 4 for medium and high level exposure groups) consistently seen across sex, racial, and educational subgroups [17••]. Observing the association of silica and autoimmune disease using different types of study designs can overcome potential biases (*eg*, recall bias, exposure misclassification) that may arise in a single study.

One important point that emerges from review of these epidemiologic studies is that the exposure assessment methods are critical. Occupational cohort studies of SLE are difficult to conduct given that SLE is a rare outcome, especially in men. Most (90%) SLE lupus patients are women, presenting a challenge since women are less likely than men to have career exposures to silica in the traditional dusty trades industries. Women may work in jobs with shorter or less intense silica exposures than typically encountered in the dusty trades. In some settings, it may be relevant to consider exposure from agricultural work [18]. Exposure assessment techniques based on assessing silica exposure in men may have low sensitivity for detecting silica exposure in studies of SLE in the general population. This can result in a biased (attenuated) effect estimate, for example, in studies that rely on death certificate coding of usual occupation. Similarly, in studies that collect job histories by interview, methods for assessing exposure can impact the likelihood of observing an association: standardized coding of silica-related job histories was much less likely to identify silica exposure than specific task-based questions in a population-based study of SLE [19••]. One way to assess the sensitivity of an exposure assessment method is to examine the sex-specific frequency of exposure among controls, which should be similar to studies in comparable populations. If the observed frequency of silica exposure is lower than expected, the assessment method is likely to be an insensitive indicator of exposure.

Another consideration in evaluating the role of silica exposure in SLE is the relevant dose required for autoimmune effects. Evidence in prior studies of silica-related autoimmune disease suggests that exposure intensity may be a more important feature than cumulative life-time exposure levels [9••]. Studies may need to consider short-term employment history with high-intensity exposures that overwhelm lung clearance mechanisms for silica, leading to higher doses in the lung-associated lymph nodes and other internal organs that have been seen to be responsible for systemic immunologic effects in animal models. Also, because silica is not metabolized or destroyed in the body, its effects may be quite long-lasting so exposure assessment should include experiences that occurred well before disease onset.

**Experimental studies**

Compared with the number of human studies, there is less experimental research directly examining the mechanisms by which silica may affect autoimmune diseases. However, the inflammatory effects of silica have long been known to play a role in the etiology of silicosis. It is well established that silica can act as an immune stimulant or adjuvant, resulting in the increased production of proinflammatory cytokines including tumor necrosis factor and interleukin-1 [9••]. This nonspecific effect is relevant given the association of silica exposure with several different autoimmune diseases. Adjuvants, in themselves, are not sufficient to produce an autoimmune disease. However, other events or processes are necessary in the generation of autoimmunity and loss of self-tolerance. In the case of silica and systemic autoimmunity, silica may also provide exposure to antigen through generation of apoptotic materials (silica is toxic to macrophages, resulting in apoptosis and necrosis). In a study of the New Zealand mixed lupus mouse strain, Brown *et al*. [20] and Pfau *et al*. [21•] showed that silica exposure exacerbated disease development (*ie*, increased autoantibody production, immune complexes, proteinuria, and glomerulonephritis), and that autoantibodies from these mice recognized specific epitopes on apoptotic macrophages.

Recent experimental studies also highlight the importance of dose or intensity of exposure, in terms of clearance from the lung and subsequent effects on other organs and on immune response. If normal clearance mechanisms are overwhelmed, as is the case with the doses required for experimental silicosis, silica-containing macrophages can be translocated to pulmonary lymph nodes and possibly more widespread throughout the lymphatic system. A study in silica-exposed rats demonstrated profound,

**Table 1. Studies of environmental exposures in relation to development of systemic lupus erythematosus in humans**

| Study | Setting and design, *n** | Exposure | Measures | Results† |
|---|---|---|---|---|
| Koeger et al. [12] | France, case-series (87 SLE patients) | Occupational silica | Work history (structured interview; 3 or more years) | Prevalence of exposure = 5% among SLE patients (no comparison group) |
| Sanchez-Roman *et al.* [13] | Spain, cohort (50) | Occupational silica | Employment in a scouring powder manufacturing plant | 3 SLE and 5 SLE/scleroderma overlap cases (more than 10 times the expected prevalence) |
| Conrad *et al.* [14] | Germany, cohort (28,000) | Occupational silica | Employment records (uranium miners) | 28 definite and 15 possible SLE cases (more than 10 times the expected prevalence) |
| Brown *et al.* [15] | Sweden, registry linkage silicosis patients (1052) | Occupational silica | Hospital discharge diagnosis of SLE | Strong association RR = 23.8 (10.3, 47.0) |
| Rosenman *et al.* [16] | Michigan, registry linkage silicosis patients (463) | Occupational silica | SLE from medical records | Highly imprecise estimate (small sample size) OR = 11.4 (0.2, 63.2) |
| Parks *et al.* [17••] | North and South Carolina, Case-control (265, 355) | Occupational silica | Work history (structured interview, any duration) | Dose response across exposure groups, medium OR = 1.7 (1.0, 3.2), high OR = 3.8 (1.2, 11.6) |
| Cooper *et al.* [30] | North and South Carolina, case-control (265, 355) | Solvents | Work history (structured interview, any duration) | No association across exposure groups, possible OR = 1.0 (0.57, 1.9), likely OR = 1.0 (0.60, 1.6) |
| Balluz *et al.* [38] | Nogales, Texas, Case-control (20, 36) | Pesticides | Biomarkers of exposures (blood) | No difference in DDE or organophosphate measures |
| Cooper *et al.* [30] | North and South Carolina, Case-control (265, 355) | Pesticides | Work history (structured interview, any duration) | Strong (but imprecise, based on small numbers) association with mixing pesticides, no association with applying pesticides, mixing: OR = 7.4 (1.4, 40.0), applying: OR = 0.77 (0.34, 1.8) |
| Rosenberg *et al.* [39] | Saskatchewan, Canada, Population-based survey (322) | Pesticides | Work and residence history and antinuclear antibodies | Low-titer (≥ 1:40) antinuclear antibodies associated with farming activities and some pesticides; no association between higher titer (≥ 1:160) antinuclear antibodies and pesticides |
| Kilburn and Warshaw [35] | Tuscon, Arizona, community survey (362) | Environmental pollutants | Antinuclear antibodies, self-reported symptoms | Increased prevalence of malar rash, seizures, arthritis/ arthalgias, and antinuclear antibodies (> 1:80 titer) compared with "nonexposed" group from Phoenix |
| Kardestuncer and Frumkin [36] | Georgia, community survey | Environmental pollutants | Prevalence and incidence of SLE | Prevalence 1000 per 100,000 persons, Incidence 63.7 per 100,000 person-years, both measures higher than expected based on other published estimates |
| Costenbader *et al.* [42••] | 7 case-control and 2 cohort studies (United States and Europe) | Behavioral smoking | Meta-analysis | Weak association with current smoking: OR = 1.5 (1.1, 2.1). No association with past smoking: OR = 0.98 (0.75, 1.3) |
| Freni-Titulaer *et al.* [44] | Georgia, case-control (44, 88) | Hair dyes (permanent type) | Structured interview, use before diagnosis | Strong association OR = 7.2 (1.9, 26.9) |
| Petri and Allbritton [45] | Baltimore, case-control (218, 186) | Hair dyes (permanent type) | Questionnaire, use before diagnosis | No association—friends as control group OR = 0.92 (0.59, 1.5); relatives as control group OR = 1.3, (0.83, 2.1) |

*For case control studies, *n* = number of cases, number of controls.
†Measures of association where given (OR, RR) followed-up by 90% confidence interval.
DDE—1,1 dichloro-2,2-bis(p-chlorophenyl) ethylene; OR—odds ratio; RR—risk ratio; SLE—systemic lupus erythematosus.

**Table 1. Studies of environmental exposures in relation to development of systemic lupus erythematosus in humans** *(Continued)*

| Study | Setting and design, *n** | Exposure | Measures | Results† |
|---|---|---|---|---|
| Reidenberg [46] | Pennsylvania, case-control (195, 143) | Hair dyes (permanent type) | Structured interview, use 1 to < 3 or 3 to 6 years before diagnosis | No association—for use 1 to < 3 years before diagnosis: friends as control group OR = 1.1 (0.6, 2.0); medical control group OR = 1.3, (0.7, 2.5). Similar results for use 3 to 6 years before diagnosis |
| Sanchez-Guerrero *et al.* [47] | Cohort study (85, 106, 391) | Hair dyes (permanent type) | Questionnaire, use before diagnosis | No association RR = 0.96 (0.63–1.5) |
| Hardy *et al.* [48] | United Kingdom, case-control (150, 300) | Hair dyes (permanent type) | Structured interview, use before diagnosis | No association OR = 1.2 (0.8, 2.0) |
| Cooper *et al.* [49] | North and South Carolina, Case-control (265, 355) | Hair dyes (permanent type) | Structured interview, use before diagnosis | Weak association OR = 1.5 (1.0, 2.2) |

*For case control studies, *n* = number of cases, number of controls.
†Measures of association where given (OR, RR) followed-up by 90% confidence interval.
DDE—1,1 dichloro-2,2-bis(p-chlorophenyl) ethylene; OR—odds ratio; RR—risk ratio; SLE—systemic lupus erythematosus.

pathologic changes in the pulmonary lymph nodes after silica dust exposure [22]. Other animal models of silicosis have shown that increases in immunoglobulin production are primarily a result of the accumulation and effects of silica in the lymph nodes [23]. Another study showed that even peritoneal macrophages can be primed by respiratory silica exposure, showing significantly stronger responses to in vitro stimulation with lippopolysaccharide than those from nonsilica exposed controls [24]. Recent studies also suggest that lymphocyte-derived interferon-gamma, which can activate macrophages and is expressed at elevated levels by lymphocytes in silicotic lymph nodes, may be responsible for the long-lasting expression of inducible nitric oxide synthase and maintenance of a chronic inflammatory state in silica-containing lymph nodes [25,26].

**Environmental exposure to silica**

Crystalline silica is a component of the particulate fraction of environmental air pollution, partially derived from soil dust and other sources [27]. It is unclear whether environmental silica exposure, at the levels experienced in the general population, is relevant to the development of autoimmune diseases, especially given the idea that peak exposures resulting in increased lymph node burden may be the most important source of systemic effects.

## Solvents

The term "solvents" represents a diverse collection of liquid compounds with different chemical properties, including alcohols, glycols, aromatic hydrocarbons (*eg*, benzene, toluene, xylene), and chlorinated products such as carbon tetrachloride and trichloroethylene [28]. Solvents are used extensively as degreasers and cleansers in many settings (*eg*, cleaning metal in a variety of industries, dry-cleaning establishments) but the specific type of solvent varies substantially across types of workplaces, has varied through time, and even varies among workplaces involved in similar activities. Exposure assessment in case-control studies is quite difficult given the diversity of products and the lack of knowledge on the part of many workers as to which specific products were used. Solvents are generally metabolized quickly so that biologic measurements reflect short-term rather than long-term or cumulative exposures.

**Epidemiologic studies**

Most of the epidemiologic studies pertaining to solvents and systemic autoimmune diseases have focused on systemic sclerosis and undifferentiated connective tissue disease [10,29]. The literature is consistent with a moderate association (ORs between 1.5 and 3.0) with the broad classification of exposure to "solvents." Trichloroethylene, mineral spirits, and petroleum-based products are some of the specific solvents that were associated with systemic sclerosis or undifferentiated connective tissue disease in some, but not all, studies. In contrast, no association was seen between occupational exposure to solvents and SLE in a recent case-control study [30] (Table 1).

**Experimental studies**

Recent experimental studies have examined the effect of trichloroethylene using lupus-prone mice [31,32,33•,34]. An acceleration of an autoimmune response (increased antinuclear antibodies and immunoglobulin production) was seen in MRL +/+ mice exposed through the drinking water to trichloroethylene or its metabolites (dichloroacetyl chloride and trichloroacetaldehyde). This effect is mediated through stimulation of CD4+ T cells and production of interferon-gamma [32,34]. Using diallyl sulfide to block the cytochrome P450 CYP2E1 metabolic pathway resulted in a reduction of the observed T–cell-mediated changes [33•]. These studies indicate that the metabolism of trichloroethylene is important in terms of effects on immune response. A limitation of this work to date is that there are no studies in strains other than MRL+/+ mice. Also, we do not know the extent to which this work, with respect to trichloroethylene, represents common effects or pathways of other types of solvents since there have been no experimental studies using other compounds.

**Environmental exposure to solvents**

Environmental exposure to various solvents can occur through contamination of the water supply. Volatile organic compounds (*eg*, benzene, formaldehyde), from industrial use and from traffic, are also air pollutants. Two community- based studies have examined lupus or lupus symptoms in relation to various forms of pollutants (Table 1). Contamination of the water supply with trichloroethylene, other solvents, and heavy metals has occurred in Tuscon, Arizona. Kilburn and Warshaw [35] reported a higher prevalence of antinuclear antibodies and self-reported symptoms related to SLE in Tucson compared with a "control" group in Phoenix, Arizona. Kardestuncer and Frumkin [36] reported a high prevalence of SLE in a small African-American community in Georgia, and hypothesized that environmental pollutants from industrial sources contributed to the disease (Table 1). These two studies provide hypotheses that need to be examined in more focused environmental epidemiology studies using newly developed methods, (*eg*, based on geographic information systems) to assess exposure to pollutants.

## Pesticides

As with solvents, "pesticides" represent a diverse group of compounds with a variety of biologic properties and modes of action. Classification of pesticides can be based on function (*eg*, herbicide, insecticide, fungicide, fumigant) and class (*eg*, triazines, organophosphates, organochlorines). The pesticides that are the most commonly used in the United States are the herbicides atrazine, glyphosate, acetochlor, and 2,4-D, the fumigants metam sodium and

methyl bromide, and the insecticide malathion [37]. Biologic measurements (*eg*, in serum or urine samples) of specific pesticides or metabolites are possible. Serologic measurements of the lipophilic compounds have the advantage of reflecting more long-term exposures.

**Epidemiologic studies**

There are few epidemiologic studies of pesticide exposure in relation to SLE (Table 1). A small case-control study in Nogales, Texas examined blood levels of DDE (the long-lasting breakdown product of the organochlorine pesticide DDT), and several organophosphate pesticide metabolites [38]. There was little difference in the distribution of these measures between cases and controls. A larger case-control study examined self-reported use of pesticides in farm-work in a rural area of the southeastern United States [30]. Mixing pesticides was relatively uncommon (reported by 8% of cases and 1% of controls who had ever lived or worked on a farm), resulting in a strong, but imprecise measure of association. No association was seen with the more common activity of pesticide application (11% of cases and 15% of controls). In a community-based study of 322 residents in Saskatchewan, the prevalence of low titer (≥ 1:40) antinuclear antibodies was associated with various farming tasks and use of some pesticides [39]. There was a two-fold increased prevalence with history of exposure to insecticides and herbicides (including specific organochlorines), but not with fungicides or algicides. The pesticide associations were not seen with higher-titer (≥ 1:160) antinuclear antibodies.

**Experimental studies**

Much of the experimental research pertaining to pesticides and immunotoxicology has focused on immunosuppressent and hypersensitivity effects [40]. Experimental studies of specific organochlorine pesticides (hexachlorobenzene) and organophosphates (malathion) have demonstrated immunosuppressive properties in conjunction with enhanced production of immunoglobulins and autoantibodies [10]. Some pesticides are endocrine-disruptors, with potential effects on steroidal hormones (estrogens, androgens, and progesterone), gonadotropin hormones, and thyroid hormones [41], but there have been no studies to date examining pesticides with respect to endocrine disrupting potential in relation to SLE.

## Smoking

A recent meta-analysis examined the association between smoking history and risk of SLE in seven case-control and two cohort studies [42••] (Table 1). The combined estimate showed a weak association with current smoking (that is, smoking around the time of diagnosis, OR 1.5, 95% confidence interval [CI] 1.1–2.1), but no association with past smoking (OR 0.98, 95% CI 0.75–1.3).

Tobacco smoke has many different effects on immune function [43]. Macrophages are activated in the alveoli, with increased myeloperoxidase activity and free-radical production. Long-term smoking may impair secretion of proinflammatory cytokines and decrease activity of natural killer cells. These, and other mechanisms, contribute to an immunosuppressive effect of smoking resulting in an increased susceptibility to infections. Smoking history has been associated with the prevalence of rheumatoid factor and antinuclear antibodies, but there is little other information available related to mechanistic issues regarding the effect of smoking on the development of autoimmune diseases in general or specifically with SLE.

Environmental tobacco smoke (passive smoking) has been studied extensively with respect to lung cancer and to cardiovascular disease, but there are no studies examining this exposure in relation to SLE or other autoimmune diseases.

## Hair Dyes

In 1989, Freni-Titulaer *et al*. [44] reported a strong association (OR 7.2, 95% CI 1.9–26.9) between use of hair dyes and other hair products and risk for SLE and other connective tissue disease, based on a small case-control study conducted in Georgia. Interest in hair dyes and other hair products was based in part on the similarities of some of the constituents of these products (arylamines) to medications involved in drug-induced lupus such as hydralazine and procainamide. Since then, several other case-control studies in a variety of settings have examined this issue [45–49], and no association or a very weak association has been seen (Table 1). In a recent analysis of hair dye use in conjunction with metabolism genes, there was an interaction between N-acetyl transferase (NAT) genotypes and use of hair dyes. A three-fold risk was seen among hair dye users who had the *10 NAT1 allele and the NAT2 slow acetylation genotype [50•]. Thus patients can be reassured that the initial report of a strong association with hair dyes has not been confirmed. If this gene–gene-exposure association is replicated in other studies, it would provide an example of the need to consider exposures in conjunction with genetic susceptibility.

## Conclusions

The role of environmental influences on the development of SLE has received relatively little attention, particularly compared with the research that has been conducted on genetics. However, the past decade has seen a number of developments in epidemiologic and experimental research with respect to some specific exposures. Respirable silica dust is an example of an occupational exposure that has been associated with several systemic autoimmune diseases, most recently with SLE. Although a general "adjuvant" effect of silica is consistent with a nonspecific effect, more experimental research aimed at eliciting mechanisms

involved in autoimmune response to silica is needed. Other experiments have examined the effect of trichloroethylene exposure in MRL +/+ mice, but there have been few epidemiologic studies of solvents in relation to SLE and no studies of other types of solvents in lupus-prone mice. Little is known regarding specific pesticides in relation to SLE, and there is little data (particularly from epidemiologic studies) pertaining to a variety of other environmental exposures, including dietary factors and stress.

Silica provides an example of a substance that is persistent in the body and generates apoptotic material in a proinflammatory environment. Many environmental agents (including ultraviolet radiation) demonstrate immune-suppressive and immune-stimulating effects. These dual effects may produce an altered response to infectious agents, such as Epstein-Barr virus, thereby indirectly leading to increased autoantibody production and possible dysregulation of the immune response. Understanding the etiology of SLE may require multidisciplinary collaborations designed to analyze the multiple interactions between environmental exposures and genetic factors (particularly genes effecting the metabolism of or response to environmental exposures).

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