

# Epidemiologic Studies of Environmental Agents and Systemic Autoimmune Diseases

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Systemic lupus erythematosus and systemic sclerosis are autoimmune diseases thought to have an exogenous trigger. This review summarizes relevant case-control and cohort studies that investigated exogenous sex hormones, silica, silicone, solvents, pesticides, mercuric chloride, and hair dyes as putative risk factors for the development of these diseases. These studies indicate that estrogen replacement therapy in postmenopausal women increases the risk of developing lupus, scleroderma, and Raynaud disease, although the increase in risk is relatively modest. Oral contraceptives may also play a role in disease susceptibility in lupus but not apparently in scleroderma. Environmental endocrine modulators, in the form of pesticides, may represent another opportunity for estrogenlike effects to occur, but there is scant evidence that these agents play a role in human systemic autoimmune disease. Although exposure to silica dust increases the risk of scleroderma in men occupied in the industry, this does not explain most male scleroderma cases. When this exposure was investigated among women, no significant risk was found. Additionally, silicone in implanted devices as well as occupational exposure to silicone-containing compounds did not pose an increased risk among women for scleroderma. The role of solvent exposure has been investigated as a risk factor for scleroderma with mixed findings. One study suggested a potential role in male patients or in those individuals with Scl-70 antibody positivity either male or female. Two other studies were unable to corroborate this finding. Mercuric chloride causes antifibrillar antibodies and immune complex glomerulonephritis in susceptible mouse strains. Antifibrillar antibodies, but not glomerulonephritis, occur in a subset of scleroderma patients and preliminary evidence suggests that mercury levels may be higher in this group of individuals. Hair products have been studied as possibly raising the risk of developing lupus, since such products contain an aromatic amine similar to a compound known to cause drug-induced lupus. A 1986 study suggested a positive association, but two subsequent studies did not support this association. *Key words:* environmental agents, estrogen, lupus, scleroderma, solvents, systemic lupus erythematosus, systemic sclerosis. — *Environ Health Perspect* 107(suppl 5): 743-748 (1999).

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Systemic lupus erythematosus (SLE, lupus) and systemic sclerosis (scleroderma) are prototypical systemic autoimmune diseases affecting multiple organ systems and characterized by the presence of autoantibodies. For the purpose of this article, the term lupus will be used to refer to the systemic form of the disease and the term discoid lupus will refer to the isolated skin disease. Similarly, the term scleroderma will be used to refer to systemic sclerosis, not to morphea or localized scleroderma that is confined to the skin. These diseases are considered autoimmune because *a*) tissue damage is mediated by immune cells and immune cell products; *b*) antibodies that recognize elements of host tissue are produced on a chronic basis; and *c*) there is no identified external stimulus against which an immune response can be considered appropriately directed. It has long been postulated that such an external stimulus exists and provides the trigger or initiating event. Persistence of disease, and perhaps its severity as well, is dependent on a complex interplay between host tissue and immune responses presumably based on genetic features. Additionally, both lupus and scleroderma have a female preponderance, with an overall female-to-male ratio

of approximately 4:1 (1,2), suggesting that sex hormones or pregnancy-related events influence disease susceptibility.

Thus, both genetic factors and sex hormones are thought to play important roles in disease risk and these features account for the occasional familial clustering and the strong female preponderance. However, these two factors together make up only a small portion of the risk, suggesting that some environmental or acquired exposure(s) is necessary for disease expression.

Interest in the possibility that environmental exposures are important in the development of scleroderma comes from compelling evidence that several pseudo-sclerodermatous conditions are triggered by the ingestion of, or exposure to, certain chemicals. For example, ingestion of contaminated rape seed oil resulted in the toxic oil syndrome in Spain in 1981 (3), and a contaminated tryptophan/protein powder nutritional supplement was associated with the eosinophilia myalgia syndrome in the United States in the late 1980s (4). Additionally, vinyl chloride disease occurred in heavily exposed workers in that industry until the syndrome was recognized and changes made to reduce the level of exposure (5). All these conditions,

however, differ in many clinical features from idiopathic scleroderma, hence the term pseudo-scleroderma or scleroderma-like conditions, and provide limited insight into the pathogenesis of systemic sclerosis.

Similarly in the case of lupus, a syndrome of drug-induced lupus is well known and associated with several widely used medications. In the drug-induced form of the disease, signs and symptoms are similar to, if not identical with, the idiopathic disease, but the drug-induced form is usually milder and symptoms remit on drug cessation.

The central issue for this review is what role, if any, environmental exposure play in idiopathic disease expression. Because of the limited value of case reports and case series, this review will focus on case-control and cohort studies. Such studies include investigations of exogenous sex hormones, silica, silicone, solvents, mercuric chloride, and hair dyes as potential risk factors for the development of these diseases.

## Exogenous Sex Hormones and the Risk of Developing Systemic Lupus

Because both lupus and scleroderma have a strong female preponderance, several studies have examined the role of female hormones in disease susceptibility. Table 1 summarizes the principal findings of these studies.

Sanchez-Guerrero et al. (6) investigated the association between postmenopausal estrogen replacement therapy and the risk of developing systemic lupus using data from the Nurses' Health Study cohort, an established cohort of women begun in 1976. These authors reported an age-adjusted relative risk (RR) for developing lupus in this group of 2.1 (95% confidence interval [CI], 1.1-4.0) for ever users of estrogen and a relative risk of 2.5 (95% CI, 2.5-5.0) for current users. Additionally, risk increased with duration of use. This analysis was based on the finding of 40 cases of definite SLE [meeting the

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**Table 1.** Sex hormones and the risk of systemic lupus erythematosus or scleroderma.

Agent	Author	RR or aOR (95% CI)	Disease
Postmenopausal estrogen	Sanchez-Guerrero et al. (25) <sup>a</sup>	RR 2.1 (1.1–4.0)	SLE
Postmenopausal estrogen > 24 months	Meier et al. (8) <sup>b</sup>	RR 2.8 (1.3–5.8)	SLE and discoid lupus
Oral contraceptives	Sanchez-Guerrero et al. (25) <sup>c</sup>	RR 1.9 (1.1–3.3)	SLE
Oral contraceptives	Strom et al. (10) <sup>d</sup>	aOR 0.6 (0.2–1.4)	SLE
Oral contraceptives	Beebe et al. (11) <sup>e</sup>	aOR 0.94 (0.74–1.22)	Scleroderma
Ever pregnant	Beebe et al. (11) <sup>e</sup>	aOR 0.86 (0.64–1.15)	Scleroderma
Postmenopausal estrogen	Beebe et al. (11) <sup>e</sup>	aOR 1.4 (1.10–1.77)	Scleroderma
Postmenopausal estrogen	Fraenkel et al. (12) <sup>f</sup>	aOR 2.5 (1.2–5.3)	Raynaud phenomenon
Postmenopausal estrogen	Fraenkel et al. (12) <sup>f</sup>	aOR 0.9 (0.3–2.6)	

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; RR, relative risk; SLE, systemic lupus erythematosus. <sup>a</sup>Nurses' Health Study cohort, based on 30 cases of SLE among 69,435 women for an incidence rate of 8/100,000 women (6). <sup>b</sup>Based on 75 cases and 295 controls in the United Kingdom (8). <sup>c</sup>Using a more stringent diagnosis of SLE than in Sanchez-Guerrero et al. (6), based on 88 cases and 121,645 controls (9). <sup>d</sup>Based on 195 cases and 143 friend controls (10). <sup>e</sup>Based on 472 scleroderma patients and 2,227 female controls by random digit dialing (11). <sup>f</sup>Based on 49 cases with Raynaud phenomenon among 497 postmenopausal women.

American College of Rheumatology criteria for the classification of lupus (7)] among 69,435 women.

Similar results were reported by Meier et al. (8), who examined the association of postmenopausal estrogen use with the development of both systemic lupus and discoid lupus, a form of lupus confined to the skin and sometimes seen as a precursor of, or concomitant condition with, the systemic form. These investigators conducted a case-control analysis based on the General Practice Research Database of the United Kingdom and the resultant series consisted of 75 cases (42 cases of SLE and 34 cases of discoid lupus) and 295 controls. The overall adjusted RR for current users versus past and nonusers was not elevated over that of controls. However, analysis of long-term users, as defined by 25 or more months of use, showed an adjusted RR estimate of 2.8 (95% CI, 1.3–5.8) for the development of SLE and discoid lupus combined. The RR in this study was adjusted for body mass index, hysterectomy, oophorectomy, and smoking status. Therapy with estrogen alone (unopposed estrogen) for greater than 24 months had an adjusted RR of 5.3 (95% CI, 1.5–18.6), whereas the combination of estrogen plus progestogen had an insignificantly elevated RR of 2.0 (95% CI, 0.8–5.0). Participants in this study were almost exclusively white; these results should be applied with caution to a nonwhite population.

These studies found no significant association of smoking status, body mass index (6,7), hysterectomy, and oophorectomy (7) with the outcome of SLE or discoid lupus.

In terms of oral contraceptive (OC) use and the risk of developing SLE, Sanchez-Guerrero et al. (9) reported a study analogous to the hormone replacement study discussed above, using the Nurses' Health Study cohort. These authors found 99 cases of definite SLE

and 88 cases of more stringently defined SLE (cases meeting the American College of Rheumatology criteria plus having a disease diagnosis by a rheumatologist) among 121,645 women in the cohort. They reported an RR of definite SLE of 1.4 (95% CI, 0.9–2.1) for past users of OCs. Using the more stringent definition of SLE, the RR was 1.9 (95% CI, 1.1–3.3). The RR estimates were adjusted for age and postmenopausal hormone use. No significant increase in risk was seen with increased duration of OC use and no significant trend was observed according to the time since first use. Because the cohort was 95% white, effects of race could not be studied and these findings may not apply to other ethnic groups.

A smaller case-control study reported by Strom et al. (10) of 195 SLE patients and 143 friend controls failed to find an association between SLE and either any use or recent use of oral contraceptives (odds ratio [OR] = 0.6; 95% CI, 0.2–1.4).

These two studies taken together suggest that the increased risk of developing SLE with oral contraceptive use is relatively small and the effect weak.

### Sex Hormones and the Risk of Scleroderma

Beebe et al. (11) studied the association between reproductive history, OC history, and estrogen replacement use in 472 female scleroderma patients and 2,227 female controls. These authors found that OC use did not influence the risk of developing scleroderma (age and year of birth adjusted odds ratio [aOR] = 0.94; 95% CI, 0.74–1.22). Additionally, earlier age of menarche (aOR = 1.00; 95% CI, 0.79–1.22) or ever being pregnant (aOR = 0.86; 95% CI, 0.64–1.15) were not associated with scleroderma.

However, estrogen replacement therapy was associated with a small but significant

increased risk of disease development with an aOR of 1.40 (95% CI, 1.10–1.77). Average age at first use was not different between cases and controls, suggesting that younger age at menopause for the cases was not responsible for this result.

Raynaud phenomenon is a reversible vasospastic condition that causes transient ischemia of the digits on cold exposure and sometimes also with emotional stress. It is most often seen as a primary condition in the absence of a connective tissue disease and affects approximately 5% of the adult American population. The autoimmune disease with which it is most frequently associated is scleroderma, in which Raynaud phenomenon affects 95% of cases. Primary Raynaud disease is seen more frequently in women than in men.

Fraenkel et al. (12) studied the association of estrogen replacement therapy and Raynaud phenomenon in 497 postmenopausal women in the Framingham Offspring Study. The prevalence of Raynaud phenomenon was 8.4% in women not taking hormone replacement therapy, 19.1% in those receiving estrogen alone, and 9.8% in those receiving estrogen plus progesterone. The aOR (adjusted for age, body mass index, use of alcohol, cigarettes, and  $\beta$ -adrenoreceptor antagonists) was 2.5 (95% CI, 1.2–5.3) with estrogen alone and 0.9 (95% CI, 0.3–2.6) with estrogen plus progesterone.

In summary, estrogen replacement therapy in postmenopausal women may increase the risk of developing lupus, scleroderma, and Raynaud disease, although the increase in risk is relatively modest. Evidence to date indicates that the addition of a progestogen to estrogen may serve to ameliorate this risk.

OCs may play a role in disease susceptibility in lupus, but evidence to date suggests this is not the case for scleroderma. It should be mentioned that these effects refer to the use of medications before disease onset and do not necessarily imply that the drugs would increase the severity of established disease.

The discussion above has concentrated on the various medical uses for exogenous estrogens as they affect the risk of autoimmune disease. There are potential environmental endocrine modulators in the form of pesticides that could also influence the risk for these diseases. Certain pesticides are known to be endocrine disruptors including polychlorinated biphenyls (PCBs), DDT metabolites, and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). PCBs exert antiestrogen activity by inhibiting estrogen-mediated signal transduction (13,14). In an analogous fashion, the longlasting metabolite of DDT (*p,p*-DDE) can bind to the androgen receptor and disrupt hormonal signaling (13). TCDD binds to the aryl hydrocarbon receptor, which also

plays a role in hormonal signaling (15). Chronic and acute exposures of mice to TCDD have suppressed total hemolytic complement and third component of complement levels, impairing host defenses to bacterial pathogens (16).

At face value, this type of immunosuppression might be considered beneficial for autoimmune disease. However, complement is needed for efficient clearing of immune complexes from the circulation and individuals with particular complement deficiencies are at a higher risk for developing lupus. Although much work has been done on the teratogenicity and immunosuppressive effects of these pesticides, little work has been done to study potential associations between these compounds and the risk for human auto-immune disease.

There is a case report of scleroderma occurring following exposure to an herbicide combination of bromobutyl methyl uracil, dichlorophenyl dimethylurea, and aminotriazole (17). Aminotriazole can cause a contact dermatitis (18), but none of these compounds have been previously associated with autoimmune disease. A case-control study of 472 female scleroderma cases and 2,227 controls found an increased risk of scleroderma in those exposed (per self-report) to herbicides and pesticides (aOR, 2.19; 95% CI, 1.16–4.15) but did not distinguish between these two exposures (19).

## Silica and Silicone

Occupational exposure to silica in the form of particulate silica dust has been associated with both the development of lupus (20) and the development of scleroderma [for review see (21)]. Such occupations include mining, sandblasting, foundry work, and grinding of certain materials. Because these occupations usually involve male workers, almost all reported cases have been male. Burns et al. (22) investigated the association between such silica exposure in women and the development of scleroderma in a case-control study involving 274 female scleroderma cases and 1,184 female controls in Michigan. There were 12 cases exposed compared to 36 controls, with an adjusted OR of 1.50 (95% CI, 0.76–2.93). Thus, although the numbers of exposed individuals are small, these data do not support an important role for silica exposure in scleroderma disease development in women.

Silman and Jones (23) found no cases of silica exposure (by self-report or by expert review as probable) among 56 male scleroderma cases in the United Kingdom.

Several epidemiologic studies have failed to find a significant association between silicone breast implants and the development of scleroderma (22,24–27). One of these studies (22) also evaluated the risk of any implanted

medical device, including pacemakers, joint prostheses, and indwelling catheters/shunts, many of which also include silicone products as part of the device. No association with scleroderma was found for these devices. Additional sources of silicone exposure through occupations and hobbies were examined by these investigators, but, again, no association was demonstrated. Silica and silicone exposure is discussed in greater detail in another article in this monograph (28).

## Solvent Exposure

The role of organic solvents and other chemicals has been suspected as contributing to disease risk in scleroderma on the basis of several case reports [(17,29–45); for review see Silman and Hochberg (46)] (Table 2).

However, when these associations were tested in case-control studies, variable results were obtained. Nietert et al. (47) reported a study involving 178 scleroderma patients and 200 controls from whom occupational histories were obtained. To assess solvent exposure, exposure scores were computed using job-exposure matrices based on a standard code. Maximum intensity of exposure and cumulative exposure were calculated. A broad category of any solvent was used as well as four specific solvents: trichloroethylene (TCE), trichloroethane (TCA), carbon tetrachloride (CCl<sub>4</sub>), and benzene. Among men (*n* = 37), those with scleroderma were more likely than controls to have a high cumulative intensity score (OR = 2.9; 95% CI, 1.1–7.6) for any solvent exposure. Men were also more likely to have a high maximum intensity score for TCE (but not other solvent) exposure (OR 3.3; 95% CI, 1.0–10.3). This effect was not seen for the women (*n* = 141). However,

if the analysis was confined to those male and female cases who had the Scl-70 autoantibody (a marker for more severe disease), significant solvent-disease associations were observed.

Somewhat at variance with these results is the report by Lacey et al. (48) of a case-control study of 472 female scleroderma patients and 2,227 controls in Ohio and Michigan, which reported a significantly increased risk of scleroderma in those with self-reported occupational activities of professional cleaning or maintenance (aOR = 2.18; 95% CI, 1.48–3.22). These activities are more likely to provide exposure to water-based solutions, than organic solvents. These investigators did not find a significant association with dry cleaning (aOR = 1.46; 95% CI, 0.91–2.34) or with TCE exposure (aOR = 2.29; 95% CI, 0.92–5.71). Paint thinners and removers were significantly associated with disease development (aOR = 1.82; 95% CI, 1.32–2.51). These last solvents are mixtures of hydrocarbons of varying molecular weights but with properties distinct from the chlorinated hydrocarbon solvents TCE, TCA, or CCl<sub>4</sub>.

Silman and Jones (23) reported an occupational analysis of 56 men with scleroderma in the United Kingdom compared to 97 controls (56 age- and geographic area-matched patients without connective tissue disease from general practitioners and 41 friend controls). Job histories and detailed descriptions and information regarding the specific agents vinyl chloride, polyvinyl chloride, silica, organic solvents, epoxy resins, and formaldehyde were obtained. Analysis was performed based on self-report as well as expert review. No significantly elevated ORs

**Table 2.** Summary of case reports and case series suggesting a relationship between environmental exposures and systemic sclerosis, exclusive of mining.<sup>a</sup>

Date of report	Author (reference)	No. of patients	Agent	Country
1957	Reinl (29)	1	Trichloroethylene	U.S.
1977	Fessel (30)	1	Welding	U.S.
1980	Yamakage et al. (31)	2	Polymerization of epoxy resins	Japan
1986	Rush and Chaiton (32)	1	Urea formaldehyde	U.S.
1987	Lockey et al. (33)	1	Trichloroethylene	U.S.
1987	Czirjak et al. (34)	8	Aromatic solvents <sup>b</sup>	Hungary
1987	Czirjak and Szegedi (35)	1	Benzene	Hungary
1988	Owens and Medsger (36)	2	<i>m</i> -Phenylenediamine	U.S.
1990	Mehlhorn et al. (37)	1	Scouring powder with crystalline silica	Germany
1991	Brasington and Thorpe-Swenson (38)	1	Organic solvents <sup>c</sup>	U.S.
1992	Pelmear et al. (39)	1	Welding	Canada
1992	Yanez-Diaz et al. (40)	1	Trichloroethylene	Spain
1992	Tibon-Fisher et al. (41)	1	Trichloromethane	Israel
1994	Dunhill and Black (17)	1	Herbicide <sup>d</sup>	England
1996	Inachi et al. (42)	1	Epoxy resins	Japan
1997	Zachariae et al. (43)	13	Organic solvents <sup>e</sup>	Denmark
1998	Attoussi et al. (44)	1	Cocaine	U.S.
1998	Biasi et al. (45)	1	Talc and heroin	France

<sup>a</sup>This table is limited to reports of systemic sclerosis, not localized scleroderma and not scleroderma-like disorders. <sup>b</sup>Various aromatic organic solvents. <sup>c</sup>Solvents included trichloroethane, xylene, trimethylbenzene, and naphthalene. <sup>d</sup>Herbicide contained bromacil or bromobutyl methyl uracil, diuron or dichlorophenyl dimethylurea, and aminotriazole. <sup>e</sup>Not well characterized.

were calculated for any category of exposure. Exposure to organic solvents was stratified on duration of use but no significant trend of increasing OR was found compared with either control group, with most ORs centering around unity. Table 3 is a summary of these results.

A study by Kilburn and Warshaw (49) reported an increase in the prevalence of some SLE symptoms as well as an increase in antinuclear bodies in a group of individuals in Tucson, Arizona, exposed to water contaminated with TCE, TCA, inorganic chromium, and other chemicals. This report is difficult to interpret because of concerns regarding exposure misclassification and case and control selection.

The role that solvents may play in disease initiation is unclear. Data from animal studies demonstrate that some solvents and/or their metabolites can bind to nucleic acids and proteins (50,51) and can reduce both the humoral and cell-mediated response (52–54). Additionally, exposure to TCE and one of its metabolites (dichloroacetyl chloride) induced autoantibody formation in genetically susceptible autoimmune-prone MRL +/+ mice (55). Byers et al. (56) studied a human population exposed to TCE in the water supply and found elevated levels of T lymphocytes as well as elevated levels of CD4<sup>+</sup> and CD8<sup>+</sup> cells, suggesting that this agent or its metabolites could alter human immunity. This study did not address the issue of autoimmune disease in this population. The role of such solvents in inducing or accelerating scleroderma or lupus remains unclear, as noted in the discussion above of the case-control studies.

## Mercuric Chloride

Mercuric chloride is an immunomodulating agent that causes immune complex glomerulonephritis and autoantibody production in

susceptible mouse strains (57,58). The autoantibody produced recognizes a nucleolar protein, fibrillarin (59). Evidence from Arnette et al. (60) suggests that mercury modifies fibrillarin leading to autoantigenicity, which then induces a persistent self-reaction to the native or unmodified fibrillarin. Antifibrillarin antibodies are found in only 8% of scleroderma patients, and, although relatively infrequent in occurrence, are associated with more severe disease.

Urinary mercury excretion has been reported to be higher in scleroderma patients who are positive for antifibrillarin antibodies than in antifibrillarin-negative patients or normal controls (61). These levels, however, were still in the normal or unexposed range, as would be expected in individuals who showed no signs or symptoms of mercury toxicity. Also, neither scleroderma patients in general nor antifibrillarin antibody-positive scleroderma patients develop immune complex glomerulonephritis.

## Hair Products

Drugs that contain aromatic amines can induce an SLE-like syndrome [for review see Price and Venables (62)]. Some hair products, including hair dyes, straighteners, and permanents, contain the aromatic amine hydrazine, some of which can be absorbed through the scalp. This observation prompted the investigation of environmental exposures to similar compounds and the risk of developing lupus. The use of hair dyes was initially reported in 1986 to increase the risk for SLE (63), but this finding has not been confirmed in two larger and more recent studies. In the 1986 study, Freni-Titulaer et al. (63) reported a positive association between hair product use and connective tissue disease in southeastern Georgia. However, in 1992 Petri and Allbritton (64)

reported their study of hair product use and the risk of development of lupus as well as the risk of having more severe disease. The patient group consisted of 218 members of the Hopkins Lupus Cohort; controls were sex-matched and age-similar relatives ( $n = 178$ ) or friends ( $n = 186$ ). The study reported no significant difference in exposure to hair dye, hair straightener, or hair permanent, and no significant differences in measures of SLE disease activity in patients who used these hair products after their diagnosis versus those who did not use the products.

Sanchez-Guerrero et al. (65), using the Nurses' Health Study Cohort (106,391 participants), found similar results, i.e., no evidence for an association between lupus ( $n = 85$  cases) and the prior use of permanent hair dye (age-adjusted RR = 0.96; 95% CI, 0.63–1.47) for ever users versus never users. Additionally, women with 15 or more years of use had no increased risk (RR = 0.92 [95% CI, 0.46–1.83]).

## Summary

There is a relative paucity of case-control or cohort studies investigating environmental exposures and the risk of developing the systemic autoimmune diseases lupus and scleroderma, in large part because these diseases are relatively rare. In total, the current state of the risk factor analysis suggests that no currently known exposure or combination of exposures explains an important proportion of the occurrence of either lupus or scleroderma. The cause of these chronic diseases is unknown and the situation is clouded by the fact that there could be multiple triggers for these diseases.

Current evidence supports the finding that estrogen replacement therapy increases the risk (approximately 1.5- to 3-fold) of developing systemic and discoid lupus, scleroderma, and Raynaud disease. The use of estrogen-progestogen combination therapy may ameliorate this risk. Oral contraceptives may double the risk for SLE, but there is lack of evidence to support this conclusion for scleroderma.

Silica exposure does not explain most male cases of scleroderma and does not appear to play a significant role in scleroderma risk in women. The role of solvent exposure, particularly in raising the risk for scleroderma in men who have a higher prevalence of such occupations, remains unclear. Hair products do not appear to raise the risk of SLE, contrary to earlier reports.

## Mechanisms

Potential mechanisms of induction of autoimmunity for these diverse environmental agents can be classified into three broad categories: *a*) a change in the hormonal

**Table 3.** Case-control studies regarding solvents and scleroderma.

Agent	Study	RR (95% CI)	Comments
All solvents	Nietert (47) <sup>a</sup>	2.9 (1.1–7.6)	Men only, cumulative intensity
Trichloroethylene	Nietert (47) <sup>a</sup>	3.3 (1.0–10.3)	Men only, maximum intensity
	Nietert (47) <sup>a</sup>	4.4 (1.3–15.0)	Scl-70-positive women, cumulative intensity
Trichloroethylene	Lacey (48) <sup>b</sup>	2.29 (0.92–5.71)	Women only, self-report
Paint thinners/removers	Lacey (48) <sup>b</sup>	1.82 (1.32–2.51)	Women only, self-report
Professional cleaning (water-based solutions)	Lacey (48) <sup>b</sup>	2.18 (1.48–3.22)	Women only, self-report
Solvents	Silman (23) <sup>c</sup>	1.7 (0.7–4.1)	Male cases/GP controls self-report
		2.3 (0.9–6.2)	Male cases/friend controls self-report
Solvents	Silman (23) <sup>c</sup>	1.3 (0.6–2.7)	Male cases/GP controls expert reviewed
Solvents	Silman (23) <sup>c</sup>	2.3 (0.9–6.2)	Male cases/friend controls

Abbreviations: CI, confidence interval; RR, relative risk. <sup>a</sup>Based on 178 scleroderma cases (37 men and 141 women) and 200 controls (60 men and 138 women); 19 women and 10 men were Scl-70 positive (47). <sup>b</sup>Based on 472 female scleroderma cases and 2,227 female controls (47). <sup>c</sup>Based on 56 male cases and 97 male controls [56 general practitioner controls and 41 friend controls (23)].

milieu to favor estrogenic stimulation of the immune system; *b*) suppression of one section of the immune system (such as complement levels), which disrupts normal immune surveillance; and *c*) chemical binding to a self-antigen forming a neoantigen, thus breaking tolerance by inducing immunity to the unmodified native molecule as well as to the modified antigen.

These mechanisms are currently speculative at best but are supported by animal models. It should be noted that the induction of autoantibodies does not necessarily result in the expression of autoimmune disease. Many of the autoantibodies are considered markers of disease with no known role in tissue damage. Several family studies have found that apparently healthy family members and even spouses of lupus and scleroderma patients may have these autoantibodies but seldom express disease. This may reflect a shared environmental exposure but the lack of the specific genes required for the "correct" immune response.

## Opportunities for Future Research

This review is relatively brief because the number of well-designed epidemiologic studies in this field is small. The existence of large population cohorts as well as an established patient cohort for scleroderma (including the Scleroderma Registry, Wayne State University, Division of Rheumatology, Detroit, Michigan) should facilitate this research. Other potential exposures such as herbicides, pesticides, and mercury, as well as exposures to infectious agents, need to be investigated. More detailed studies of occupational and environmental exposures are clearly warranted by preliminary data and are currently feasible given the interest of the scientific community and availability of large patient cohorts.

## REFERENCES AND NOTES

- Mayes MD, Laing TJ, Gillespie BW, Cooper B, Lacey J Jr, Hirschenberger W, Atty S, Schottenfeld D. Epidemiology of scleroderma in the Detroit Tricounty area 1989–1991: prevalence, incidence and survival [Abstract]. *Arthritis Rheum* 39:S150 (1996).
- Masi AT, Kaslow RA. Sex effects in systemic lupus erythematosus: a clue to pathogenesis. *Arthritis Rheum* 21:480–484 (1978).
- Alonso-Ruiz A, Zea-Mendoza AC, Salazar-Vallinas JM, Rocamora-Ripoll A, Beltran-Gutierrez J. Toxic oil syndrome: a syndrome with features overlapping those of various forms of scleroderma. *Semin Arthritis Rheum* 15:200–212 (1986).
- Hertzman PA, Blevins WL, Mayer J. Association of the eosinophilia-myalgia syndrome with the ingestion of tryptophan. *N Engl J Med* 322:869–873 (1990).
- Harris DK, Adams WGF. Acroosteoecolysis occurring in men engaged in the polymerisation of vinyl-chloride. *Br Med J* 3:712–714 (1967).
- Sanchez-Guerrero J, Liang, MH, Karlson, EW, Hunter, DH, Colditz, GA. Postmenopausal estrogen therapy and the risk of developing systemic lupus erythematosus. *Ann Intern Med* 122:430–433 (1995).
- Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JS, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25:1271–1277 (1982).
- Meier CR, Sturkenboom MCJM, Cohen AS, Jick H. Postmenopausal estrogen replacement therapy and the risk of developing systemic lupus erythematosus or discoid lupus. *J Rheumatol* 25:1515–1519 (1998).
- Sanchez-Guerrero J, Karlson EW, Liang MH, Hunter DJ, Speizer FE, Colditz GA. Past use of oral contraceptives and the risk of developing systemic lupus erythematosus. *Arthritis Rheum* 40:804–808 (1997).
- Strom BL, Reidenberg MM, Snyder ES, Freundlich B, Stolley PD. Shingles, allergies, family medical history, oral contraceptives, and other potential risk factors for systemic lupus erythematosus. *Am J Epidemiol* 140:632–642 (1994).
- Beebe JL, Lacey JV Jr, Mayes, MD, Gillespie BW, Cooper BC, Laing TJ, Schottenfeld D. Reproductive history, oral contraceptive use, estrogen replacement therapy and the risk of developing scleroderma [Abstract]. *Arthritis Rheum* 40:S100 (1997).
- Fraenkel L, Zhang Y, Chaisson CE, Evans SR, Wilson PWF, Felson DT. The association of estrogen replacement therapy and the Raynaud phenomenon in postmenopausal women. *Ann Intern Med* 129:208–211 (1998).
- Shekhar PV, Werdell J, Basur VS. Environmental estrogen stimulation of growth and estrogen receptor function in preneoplastic and cancerous human breast cell lines. *J Natl Cancer Inst* 89:1774–1782 (1997).
- Bergeron JM, Crews D, McLachlan JA. PCBs as environmental estrogens: turtle sex determination as a biomarker of environmental contamination. *Environ Health Perspect* 102:780–781 (1994).
- Tian Y, Ke S, Thomas T, Meeker RJ, Gallo MA. Transcriptional suppression of estrogen receptor gene expression by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). *J Steroid Biochem Mol Biol* 67:17–24 (1998).
- White KL Jr, Lysly HH, McCay JA, Anderson AC. Modulation of serum component levels following exposure to polychlorinated dibenzo-*p*-dioxins. *Toxicol Appl Pharmacol* 84:209–219 (1986).
- Dunnill MGS, Black MM. Sclerodermatous syndrome after occupational exposure to herbicides—response to systemic steroids. *Clin Exp Dermatol* 19:518–520 (1994).
- English JSC, Rycroft RJG, Calnan CD. Allergic contact dermatitis from aminotriazole. *Contact Derm* 14:255–256 (1986).
- Laing T, Gillespie B, Burns C, Garabrant D, Heeringa S, Alcser K, Schottenfeld D, Mayes M. Risk factors for scleroderma among Michigan women [Abstract]. *Arthritis Rheum* 38:S341 (1995).
- Conrad K, Mehlhorn J, Luthke K, Dorner T, Frank KH. Systemic lupus erythematosus after heavy exposure to quartz dust in uranium mines: clinical and serological characteristics. *Lupus* 5:62–29 (1996).
- Haustein UF, Anderegg U. Silica-induced scleroderma—clinical and experimental aspects. *J Rheumatol* 25:1918–1926 (1998).
- Burns CJ, Laing TJ, Gillespie BW, Heeringa SG, Alcser KH, Mayes MD, Wasko MCM, Cooper BC, Garabrant DH, Schottenfeld D. The epidemiology of scleroderma among women: assessment of risk from exposure to silicone and silica. *J Rheumatol* 23:1904–1911 (1996).
- Silman AJ, Jones S. What is the contribution of occupational environmental factors to the occurrence of scleroderma in men? *Ann Rheum Dis* 51:1322–1324 (1992).
- Gabriel SE, O'Fallon WM, Kurland LT, Beard CM, Woods JE, Meltan LJ III. Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med* 330:1697–1702 (1994).
- Sanchez-Guerrero J, Colditz GA, Karlson EW, Hunter DJ, Speizer FE, Liang MH. Silicone breast implants and the risk of connective tissue diseases and symptoms. *N Engl J Med* 332:1666–1670 (1995).
- Hochberg MC, Perlmutter DL, Medsger TA Jr, Nguyen K, Steen V, Weisman MH, White B, Wigley FM. Lack of association between augmentation mammoplasty and systemic sclerosis. *Arthritis Rheum* 39:1125–1131 (1996).
- Hennekens CH, Lee I-M, Cook NR, Hupert PR, Karlson EW, LaMotte F, Manson JE, Buring JE. Self-reported breast implants and connective tissue diseases in female health professionals. A retrospective cohort study. *JAMA* 275:616–621 (1996).
- Hattori A. Unpublished data.
- Reini W. Scleroderma caused by trichloroethylene? *Bull Hygiene* 32:678–679 (1957).
- Fessel WJ. Scleroderma and welding [Letter]. *N Engl J Med* 296:1537 (1977).
- Yamakage A, Ishikawa H, Saito Y, Hattori A. Occupational scleroderma-like disorders occurring in men engaged in the polymerization of epoxy resins. *Dermatologica* 161:33–44 (1980).
- Rush PJ, Chaiton A. Scleroderma, renal failure, and death associated with exposure to urea formaldehyde foam insulation. *J Rheumatol* 13:475–477 (1986).
- Lockey JE, Kelly CR, Cannon GW, Colby TV, Aldrich V, Livingston GK. Progressive systemic sclerosis associated with exposure to trichloroethylene. *J Occup Med* 29:493–496 (1987).
- Czirjak L, Danko K, Schlamadinger J, Suranyi P, Tamasi L, Szegegi GY. Progressive systemic sclerosis occurring in patients exposed to chemicals. *Int J Dermatol* 26:374–378 (1987).
- Czirjak L, Szegegi G. Benzene exposure and systemic sclerosis [Letter]. *Ann Int Med* 107:118 (1987).
- Owens GR, Medsger TA. Systemic sclerosis secondary to occupational exposure. *Am J Med* 85:114–116 (1988).
- Mehlhorn J, Gerlach C, Ziegler V. Berufsbedingte progressive systemische Sklerodermie durch ein quarzhaltiges Scheuremittel. *Dermatosen* 38:180–184 (1990).
- Brasington RD Jr, Thorpe-Swenson AJ. Systemic sclerosis associated with cutaneous exposure to solvent: case report and review of the literature. *Arthritis Rheum* 34:631–633 (1991).
- Pelmear PL, Roos JO, Maehle WW. Occupationally-induced scleroderma. *J Occup Med* 34:20–25 (1992).
- Yanez-Diaz S, Moran M, Unamuno P, Armijo M. Silica and trichloroethylene-induced progressive systemic sclerosis. *Dermatology* 184:98–102 (1992).
- Tibon-Fisher O, Heller E, Ribak J. Occupational scleroderma due to organic solvent exposure [in Hebrew]. *Harefuah* 122:530–532 (1992).
- Inachi S, Mizutani H, Ando Y, Shimizu M. Progressive systemic sclerosis sine scleroderma which developed after exposure to epoxy resin polymerization. *J Dermatol* 23:344–346 (1996).
- Zachariae H, Bjerring P, Sondergaard KH, Halkier-Sorensen L. Occupational systemic sclerosis in men [in Danish]. *Ugeskrift for Laeger* 159:2687–2689 (1997).
- Attoussi S, Faulkner ML, Oso A, Umoro G. Cocaine-induced scleroderma and scleroderma renal crisis. *Southern Med J* 91:961–963 (1998).
- Biasi D, Carletto A, Caramaschi P, Pacor ML, Zeminian S, Bambera LM. Can talc mixed with heroin induce systemic sclerosis [Letter]? *Rev Rhumatisme (English)* 65:157–158 (1998).
- Silman AJ, Hochberg MC. Occupational and environmental influences on scleroderma. *Rheumatic Dis Clinics NA*. 22:737–750 (1996).
- Nieter PJ, Sutherland SE, Silver RM, Pandy JP, Knap RG, Hoel DG, Dosemeci M. Is occupational organic solvent exposure a risk factor for scleroderma? *Arthritis Rheum* 41:1111–1118 (1998).
- Lacey JV Jr, Garabrant DH, Gillespie BW, Cooper BC, Laing TJ, Mayes MD, Schottenfeld D. Self-reported exposure to solvents in women with systemic sclerosis (SSc) [Abstract]. *Arthritis Rheum* 40:S201 (1997).
- Kilburn KH, Warshaw RH. Prevalence of symptoms of systemic lupus erythematosus (SLE) and of fluorescent antinuclear antibodies associated with chronic exposure to trichloroethylene and other chemicals in well water. *Environ Res* 57:1–9 (1992).
- Bolt H, Filser J. Irreversible binding of chlorinated ethylenes to macromolecules. *Environ Health Perspect* 21:107–112 (1977).
- Rocci P, Prodi G, Grilli S, Ferreri A. In vivo and in vitro binding of carbon tetrachloride with nucleic acids and proteins in rat and mouse liver. *Int J Cancer* 11:419–425 (1973).
- Sanders VM, Tucker AN, White KL, Kauffmann BM, Hallett P, Carchman RA, Borzelleca JF, Munson AE. Humoral and cell-mediated immune status in mice exposed to trichloroethylene in the drinking water. *Toxicol Appl Pharmacol* 62:358–268 (1982).
- Kauffmann BM, White KL, Sanders VM, Douglas KA, Sain LE, Borzelleca JF, Munson AE. Humoral and cell-mediated immune status in mice exposed to chloral hydrate. *Environ Health Perspect* 44:147–151 (1982).
- Shopp G, Sanders V, White K, Munson A. Humoral and cell-mediated immune status of mice exposed to *trans*-1,2-dichloroethylene. *Drug Chem Toxicol* 8:393–407 (1985).
- Khan MF, Kaphalia BS, Prabhakar BS, Kanz MF, Ansari GA. Trichloroethylene-induced autoimmune response in female MRL *+/+* mice. *Toxicol Appl Pharmacol* 134:155–160 (1995).
- Byers V, Levin A, Ozonoff D, Baldwin R. Association between clinical symptoms and lymphocyte abnormalities in a population with chronic domestic exposure to industrial solvent-contaminated domestic water supply and a high incidence of leukaemia. *Cancer Immunol Immunother* 27:77–81 (1988).
- Robinson CJ, White HJ, Rose NR. Murine strain differences in response to mercuric chloride: antinuclear antibodies production does not correlate with renal immune complex deposition. *Clin Immunol Immunopathol* 83:127–138 (1997).

58. Hanley GA, Schiffenbauer J, Sobel ES. Resistance to HgCl<sub>2</sub>-induced autoimmunity in haplotype-heterozygous mice is an intrinsic property of B cells. *J Immunol* 161:1778-1785 (1998).
59. Pollard KM, Lee DK, Casiano CA, Bluther M, Johnston MM, Tan EM. The autoimmunity-inducing xenobiotic mercury interacts with the autoantigen fibrillarin and modifies its molecular and antigenic properties. *J Immunol* 158:3521-3528 (1997).
60. Arnett FC, Reveille JD, Goldstein R, Pollard KM, Leaird K, Smith EA, Leroy EC, Fritzler MJ. Autoantibodies to fibrillarin in systemic sclerosis (scleroderma). An immunogenetic, serologic, and clinical analysis. *Arthritis Rheum* 39:1151-1160 (1996).
61. Arnett FC, Fritzler MJ, Ahn C, Hollan A. Urinary mercury (Hg) levels in systemic sclerosis (SSc): possible association with anti-fibrillarin autoantibodies [Abstract]. *Arthritis Rheum* 49:S103 (1998).
62. Price EJ, Venables PJ. Drug-induced lupus. *Drug Safety* 12:283-290 (1995).
63. Freni-Titulaer LWJ, Kelley DB, Grow AG, Mckinley TW, Arnett FC, Hochberg MC. Connective tissue disease in southeastern Georgia: a case-control study of etiologic factors. *Am J Epidemiol* 130:404-409 (1989).
64. Petri M, Allbritton J. Hair product use in systemic lupus erythematosus. *Arthritis Rheum* 35: 625-629 (1992).
65. Sanchez-Guerrero J, Karlson EW, Colditz GA, Hunter DJ, Speizer FE, Liang MH. Hair dye use and the risk of developing systemic lupus erythematosus. *Arthritis Rheum* 39:657-662 (1996).