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Pesticides, chemical and industrial exposures in relation to systemic lupus erythematosus

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Abstract

Growing evidence suggests exposure to chemicals and industrial pollutants may increase risk of SLE. Here we review research on SLE associations with occupational and industrial exposures, primarily drawing on studies in human populations and summarizing epidemiologic research published in the past decade. The association of occupational silica exposure with SLE is well established, but key questions remain, including the required dose and susceptibility factors, and SLE risk due to other silicate exposures. Research on SLE and other exposures is less well developed, though several potential associations merit further consideration due to the consistency of preliminary human findings, experimental animal research, and biologic plausibility. These include pesticides and solvents, for which experimental findings also support investigation of specific agents, including organochlorines and trichloroethylene. Experimental findings and biologic plausibility suggest research on SLE and occupational exposure to hydrocarbons (i.e., mineral oils) is warranted, especially given the widespread exposures in the population. Experimental and limited human findings support further investigation of SLE related to mercury exposure, especially in dental occupations. Research on environmental risk factors in risk-enriched cohorts (family based) is recommended, as is further investigation of exposures in relation to intermediate markers of effect (e.g., antinuclear antibodies), clinical features (e.g., nephritis) and outcomes.

Keywords

Systemic Lupus Erythematosus; environmental risk factors; occupational exposures; silica; pesticides; epidemiology

Systemic lupus erythematosus (SLE) is a complex disease caused by interactions of intrinsic susceptibility with environmental risk factors. Growing evidence supports the idea that risk of developing SLE may be increased by exposure to chemicals and industrial pollutants. Here we review research on the risk of SLE associated with occupational and environmental exposures, primarily drawing on studies in human populations, along with supportive

findings from experimental studies and relevant research on related systemic autoimmune diseases. We review the evidence on (1) silica and silicates, (2) agricultural and residential pesticides, (3) solvents and other hydrocarbons, and other occupational exposures and summarize relevant findings from several studies published in the past decade (Table 1) (1–6). The biologic mechanisms leading to development of autoimmunity and progression to clinical SLE are not fully understood, but it seems plausible that exposures may have effects at different points in these processes (7). Thus, we also consider findings on exposure-associated autoantibodies.

Exposures

Silica and silicates

Exposure to crystalline silica (quartz) dust is a widespread occupational hazard, with the highest exposures in construction, mining, ceramics, stone masonry or tile work, and certain manufacturing processes. Previous reviews have extensively documented the body of research showing that silica is a risk factor for SLE and other systemic autoimmune diseases (7–9). In brief, evidence over the past century has evolved from descriptions of systemic sclerosis in stone masons, to several studies in the 1990s describing associations of high level silica exposure with SLE, rheumatoid arthritis and systemic sclerosis in large case series, registry linkage studies and occupational cohorts. In the past decade, 3 case-control studies of SLE have specifically assessed occupational silica exposure, describing dose-response associations of SLE by increasing intensity (10), duration (3), and number of different types of exposure sources (4). These findings are confirmed in very large, population-based studies using less specific methods for case ascertainment and exposure classification, which reported increased death or hospitalization with SLE in association with specific occupations with potentially high-level silica (5, 6), including mining machine operators (OR=1.8), dental hygienists (OR=3.0), miners and quarry workers (SIR=5.0), electrical workers (SIR=1.6), other construction workers (SIR=2.1), glass ceramic and tile workers (SIR=4.4), and chimney sweeps (SIR=4.5).

The weight of the evidence supports silica as a likely cause of SLE, but important questions remain. These include the role of susceptibility factors. Smoking has been an inconsistent modifier of silica effects on SLE across three studies (3, 4, 10). Genetic risk factors for other silica-associated diseases (e.g., cytokine polymorphisms and silicosis) have been considered (11–13), but it is not known whether genetically susceptible individuals can be identified for risk of silica-associated SLE. Another key question is the required silica dose for development of SLE (and other autoimmune outcomes). Apparent dose effects have been suggested in human studies, across variable metrics: it is not clear whether greater intensity or duration of exposure is of most importance. While high level silica exposure is an established occupational risk factor for silicosis, better understanding is needed of the required dose for silica to impact SLE risk, to determine whether additional measures are needed to protect workers. Given the differences in human and experimental exposure scenarios, it is unclear the extent to which experimental studies may help determine required dose parameters. Thus, more human studies with detailed exposure data will be needed to identify relevant dose characteristics and susceptibility factors.

Experimental studies on silica and autoimmunity in animal models have followed the growing collection of human data, and have been recently reviewed elsewhere (7, 14). These suggest plausible mechanisms relating silica to SLE; a likely scenario is that inhaled silica (respirable dust) becomes trapped in the lung and other tissues, and the resulting cycle of apoptosis, together with increased exposure to self-antigens and inflammation, may lead to development or acceleration of autoimmunity. Silica appears to be a non-specific risk factor for SLE and other systemic autoimmune diseases, and it is not known why some individuals may develop lupus instead of another autoimmune disease. Studies have shown elevated antinuclear autoantibody levels associated with silica exposure (reviewed by Parks and Cooper, 2006) (9), though not consistently (15, 16). While a minority of those with autoantibodies go on to develop SLE, specific factors that may determine progression to SLE remain unexplored. Expanded research across different animal models (including both standard lupus models and non-autoimmune prone mice) may be useful in addressing dose and route of exposure (17), and genetic risk factors for progression of silica-related autoimmunity into clinical autoimmune diseases.

In addition to silica, industrial exposures to other silicates may act in a similar way to increase SLE risk. Asbestos, a long-chain silicate, has been examined as a risk factor for several systemic autoimmune diseases in Libby, Montana, a community contaminated with asbestos due to vermiculite mining (OR 2.1; 95% CI 0.9, 5.1 combined across rheumatoid arthritis, systemic sclerosis, and SLE). Occupational asbestos exposure was associated with RA in men (OR 2.5; 95% CI 1.0, 6.8), but not in women (18). Further research has shown a higher rate of antinuclear antibodies in Libby residents compared to a neighboring community (19), and an increased likelihood of pleural abnormalities in Libby residents with antinuclear antibodies (suggesting a correlation with asbestos exposure) (20). Studies in mice suggest Libby amphibole asbestos may be related to elevated autoantibodies and response to apoptotic materials (21, 22). Experimental findings in Lewis Rats exposed to Libby asbestos indicated a non-dose response association of exposure with development of ANA and proteinuria (23, 24). Notably, kidney pathology in these animals was normal, no anti-dsDNA antibodies were observed, and increased ANA prevalence appeared to be primarily a response to the Jo-1 antigen (associated with interstitial lung disease in humans). Given the longstanding and ongoing global industrial exposures to silica and silicates, further investigation of their effects on SLE risk is warranted.

Agricultural and residential pesticides

Pesticides have been suspected as a cause of SLE because of epidemiologic studies reporting increased risks of RA and limited evidence of an elevated risk of SLE associated with farm work or farm history (5, 10, 18, 25–27)). In the Carolina Lupus Study, full-time farm work for at least 12 months was associated with SLE (10). A large analysis of death records found 20% increased risk of death with SLE among persons with farming listed as their ‘usual occupation’ on the death certificate (5). This risk increase was attributable to farming in the crop industry (OR=1.3), and there was no risk associated with farming in the livestock industry (OR=0.9). In contrast, men occupied as farmers in Sweden were significantly less likely than those in the general population to be hospitalized with SLE (6), though this decrease in risk was primarily within 10–20 years of follow-up and was not seen 20+ years

after occupations were recorded. These discrepancies may reflect the inherent challenges of these types of study design, for which there are no data on disease onset relative to the initiation and duration of occupational exposures, and the likelihood of a “healthy worker” effect by which ill workers may self-select themselves out of certain types of occupations.

Fewer studies have evaluated risk associated with pesticide exposure, per se, whether in farming or in other settings. A history of mixing pesticides for agricultural work in the southeastern US was associated with development of SLE (OR=7.4), based on exposure in 8% of SLE cases and 1% of controls (2), and with a non-significant 2.3-fold increased risk of high-titer ANA among controls (28). In this same sample, there was no association of SLE with application of pesticides, an activity presumed to involve lower exposures than mixing (2). However these analyses did not adjust for other agricultural exposures (other than silica), including organic dust (livestock/grain dust) exposure (1), which was later identified as potentially protective factor. Another case-control study conducted through rheumatology centers across Canada did not find any association with occupational pesticide use (4). In a prospective cohort study of post-menopausal women, ages 50 to 79 years, those who reported ever personally mixing/applying insecticides (mostly in a residential setting) had increased risk of developing SLE during the study follow-up (there were 35 incident SLE cases), with trends of increasing risk by cumulative use (frequency×duration; p-trend 0.06) (25); a similar pattern was observed with insecticide application by others (p-trend=0.10). Because of the sample characteristics (older, post-menopausal), it is unclear whether these findings can be generalized to SLE cases occurring in reproductive age women.

Despite the general associations noted for pesticides and SLE in some studies, none have examined specific pesticide classes or products, which may be more easily studied in cohorts with detailed exposure data (including measured levels in blood) or in animal models. Insecticide exposure was associated with low-titer ANA positivity in a cross-sectional study of 322 rural residents in Saskatchewan, Canada (29), whereas there was no significant association with other classes of pesticides, including herbicides and fungicides. Specifically, only pyrethroid insecticides and oilseed production were associated ANA positivity in a multivariate model including various pesticides and crops. Another analysis within the same Canadian study suggested decreased ANA prevalence in men with elevated plasma bromoxynil and recent occupational use of 2,4-dichlorophenoxyacetic acid (30). These studies highlight the diversity of exposures in a farm environment and the need to control for potential confounding. The extent to which ANA findings can be extended to risk of SLE is not known, however these findings do show that the effects of pesticides on autoimmunity are likely to be complex and identifying specific pesticides as causal risk factors may be challenging.

Intriguing evidence for an association between organochlorine insecticides and development of SLE comes from experimental studies, in which treatment with chlordecone, methoxychlor, or o,p'-DDT accelerated SLE disease onset including earlier elevated autoantibody levels and renal impairment in lupus-prone mice (31, 32), but not in a non-susceptible mouse strain (33). Prevalence of ANA in North Carolina African-American farmers was somewhat elevated in those with the highest measured blood levels of p,p'-

DDE (major metabolite of DDT; OR=1.9, 0.3–11.3), but this estimate was based on few participants (34). Two small epidemiologic studies have compared blood concentration of organochlorine pesticides/metabolites between SLE cases and controls. There was no difference between cases and controls for DDE in a small study conducted the southwestern US (35); however, a number of issues limit inference from this study, most notably inclusion of prevalent (rather than newly diagnosed) cases and the fact that both cases and controls had higher than average pesticide levels compared to the US general population. A study conducted in Delhi, India found significantly higher blood levels of p,p'-DDE, dieldrin, beta-endosulfan, and beta-hexachlorocyclohexane in 13 SLE cases than in 20 healthy controls (36); there was no difference in the other organochlorine pesticides measured. Overall, inferences based on existing epidemiologic data on SLE risk associated with pesticides are limited due to inconsistent results and because no specific pesticide or product has been identified as a likely causal agent. The most convincing data on specific pesticides come from animal studies of organochlorine insecticides; the fact that most of these pesticides are banned or highly restricted diminishes the opportunities for continued research of these compounds. At the same time, because they are persistent in the environment and continue to be used for vector control in some countries, organochlorine exposures will continue to occur in the future at lower levels and in different settings.

Solvents and other hydrocarbons

Hydrocarbons are a broad group of organic compounds with diverse industrial uses, including products such as fuels, solvents, lubricants, emulsifiers or waxes. Organic solvents are in widespread use in workplace and residential settings as cleaners (as in dry cleaning, industrial degreasing, and in nail polish removers) and in chemical formulations (as in paints, varnishes, and perfumes). There have been numerous investigations of organic solvents as a potential cause of autoimmune diseases, and strong and consistent links have been reported with systemic sclerosis (37); however, only a few studies have investigated the association of solvents with SLE. Across different studies and study designs, increased SLE risk has been associated with jobs and tasks that typically entail solvent exposure: elevated SLE mortality associated with hand painting, coating, and decorating (OR=3.7), garage and service station-related occupations (OR=2.3) (5); higher SLE hospitalization in artistic workers (SIR men=2.5), and shoe and leather workers (SIR men=6.9) (6); and a case-control study showing higher odds of SLE for history of being an artist working with paints (OR=3.9), work with dyes or developing film (OR=3.9), repairing or cleaning machinery or metal (OR=1.9), applying nail polish or nail applications (OR=10.2), and dry cleaning (OR=1.5) (4). However, the two studies that rigorously assessed solvent exposure based on detailed job histories and additional questions on solvent use and high-exposure work tasks found no overall or dose-response associations with SLE (2, 3). Despite these inconsistent results, continued use of solvents in work and residential settings and a convincing role of solvents in the etiology of other autoimmune diseases justify further research on solvents in relation to SLE. Examination of risk associated with specific types of solvents will be the most informative strategy if there appears to be no global risk associated with all solvents as a broad category. Studies of lupus-prone mice provide strong evidence of an accelerated autoimmune response from dosing with trichloroethylene, including accelerated autoantibody expression, T-cell activation, and secretion of inflammatory

cytokines (as reviewed by Cooper 2009) (7). Similar cytokine changes have been seen in humans with occupational or environmental exposure to trichloroethylene (38), suggesting that future SLE research with careful characterization of trichloroethylene exposure may be fruitful.

Dioxins, furans, polychlorinated biphenyls (PCBs), and other polycyclic aromatic hydrocarbons are widespread organic pollutants that are persistent in the environment and bioaccumulate in the food chain. These organohalogens have varying mechanisms of biologic activity and toxicity, the most well-characterized of which are immunosuppressive effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and other dioxin-like congeners, instigated by binding to the arylhydrocarbon receptor. Increased SLE mortality was observed in long-term follow-up of a Taiwanese population accidentally exposed to high levels of PCBs and furans through consumption of contaminated rice, with SLE deaths starting 10 years after the exposure (39). Development of a lupus-like syndrome has been observed in two different strains of mice (C57BL/6 and SNF (1)) following mid-gestation dosage with TCDD, with some differences in effect by sex (40, 41). In contrast, a study of New Zealand Black/New Zealand White F1 hybrid (B/W) mice injected with TCDD since 6 weeks of age found exposure to be suppressive of SLE disease activity (32). It is possible that these ubiquitous organohalogen pollutants increase the risk of SLE; but more study is needed, including human studies considering the timing of exposures at different developmental periods, as well as both animal and human studies considering potential effects of other, non-dioxin like organohalogens.

Mineral oils are broadly classified mixtures of alkanes and cyclic paraffins, typically byproducts of petroleum distillation or production from crude oil. Mineral oils have diverse industrial uses, including as a hydraulic fluid, as cutting or lubricating oils, production of cosmetics and food, and agricultural prevention of scale and mites on plants or animals. In addition to occupational exposures, mineral oils are a widespread component of cosmetics and lotions, and can be an environmental contaminant as an industrial byproduct. Mineral oils are poorly degraded and are well known for their use as adjuvants in vaccine production to boost antibody responses. Human exposures can lead to granulomas in liver, spleen and lymph nodes, and low molecular weight mineral oils (e.g., pristane) are well known for their ability to induce lupus-like disease in animal models and stimulate lupus-like autoantibodies in non-autoimmune prone mice (42, 43). Despite potentially widespread exposures, we could find no study that examined mineral oil as a risk factor for SLE; however, occupational exposure to mineral oils was associated with rheumatoid arthritis in one study (44). Researchers have also investigated a cluster of SLE cases in the Southwestern U.S. in a neighborhood built on an abandoned oil field waste site (45), with documented personal and residential exposure and high rates of SLE compared to national prevalence estimates. Inferences from this study are limited, however, by the fact that the study did not systematically assess SLE in the population and also given the high percentage of Hispanics in the study sample (a possible concern given documented clustering of U.S. SLE mortality related to Hispanic ethnicity) (46). Based on the extensive findings in animal studies and widespread nature of the exposure, however, further investigations of mineral oil exposure in relation to human SLE are warranted.

Other occupational and industrial risk factors

Occupational settings provide a unique opportunity to consider environmental risk factors, as increased risk may be most readily identified in jobs with high-level or long-term exposures to specific agents. Silica is the best example of a risk factor for systemic autoimmune diseases that was first observed in cohorts of workers exposed to very high levels of silica (i.e., those typically associated with risk of silicosis), and was later confirmed in studies of the general population with more diverse occupational exposures. Other occupational associations with SLE may provide clues for future research and suggest new avenues for investigating specific exposures. Experimental studies show that mercury and other heavy metals may increase systemic autoimmunity (47–49), and may increase risk associated with other exposures (50). In humans, elevated ANA have been seen in a one study of mercury-exposed gold miners (51), and two case-control studies have shown elevated risk of SLE associated with self-reported exposure to mercury (2, 4). Endotoxins are another important class of immune adjuvants, present in organic dusts across a variety of industries. An association with SLE is suggested by one large study showing SLE mortality was associated with work as a textile machine operator (OR=1.5) (5). However, no overall association was seen for work in textiles in the one case-control study to specifically ask about textile work (1). In sum, these findings, though limited, support further research on mercury and organic dust exposures.

Summary and discussion

The association of occupational silica exposure and lupus is well established, especially in light of findings on other systemic autoimmune diseases. Key questions remain, including the required dose and susceptibility factors, and extension of risk to include other related silicates. Research linking SLE with other exposures is less well developed, though several potential associations merit further consideration either due to the consistency of preliminary human data and/or biologic plausibility arising from experimental studies. Findings for pesticide use are intriguing, given the consistency of evidence from farming and other sources with rheumatoid arthritis; organochlorine pesticides are a potential candidate exposure based on experimental studies and limited human data. Similarly, SLE associations with solvents are supported by experimental data suggesting trichloroethylene as a specific risk factor and a few suggestive studies for certain occupational groups. Findings on other hydrocarbons, i.e., mineral oils, stems primarily from animal models, with very limited human data despite widespread exposures.

Case ascertainment and exposure assessment

Efforts to discern the effects of environmental factors on SLE risk are limited by several challenges, including the lack of systematic patient registries (as there are for cancer), which help researchers to accurately and efficiently identify cases. Thus, ascertainment of SLE cases in large cohorts may be limited to linkage to death certificate data or claims data, both of which are limited in ability to accurately or comprehensively identify cases in the population. Self-reported SLE status in smaller cohorts is likely to include a majority of false positives (52), but can be supplemented by data on disease-specific medication use. The case-control design offers greater opportunity to accrue larger numbers of validated

cases, but requires retrospective exposure assessment. Indeed, assessing and quantifying exposures in epidemiologic studies poses another a major challenge for researchers. In studies of SLE, where the female predominance may limit the frequency of certain high exposure jobs (e.g., such as work in construction, a source of silica exposure), striving for accuracy in exposure assessment is of utmost importance. Rare or lower level exposures are more difficult to assess and effects more difficult to identify. Further description and suggested methods for exposure assessment have been previously reviewed (9).

Pre-clinical or asymptomatic autoimmunity

The duration of preclinical autoimmunity may extend years prior to SLE symptoms onset and clinical diagnosis (i.e., antinuclear antibodies were seen at a 1:120 dilution up to 9 years prior to diagnosis in a majority of patients identified in a military cohort) (53). However, the etiologic role of autoantibodies and mechanisms leading to disease initiation and promotion are not well established. Thus, the relevant time window for etiologic exposures is difficult to elucidate and may limit interpretation of null findings from human studies. Preclinical autoimmunity allows researchers to examine risk factors for autoantibodies, which provides some advantages over studying incident disease, given their relatively high frequency in the population. Such studies may focus on populations with high levels of specific chemical or industrial exposures, such as occupational cohorts, although most occupational cohorts do not prospectively collect or store clinical samples. Studies may also be designed to examine the role of proximal exposures in the development of lupus, for example, through characterizing exposures in cases with preclinical sera or in enriched risk populations (such as family members). Adding detailed occupational and exposure data increases the value of family-based studies with genotype data and long-term follow-up due to the increased power of these designs to detect gene-environment interactions.

Disease phenotype and outcomes

There is a lack of general data on the role of occupational exposures on SLE progression or outcomes. Some exposures, such as silica, may promote disease through ongoing processes in the lung or other organs. Kidney disease has been associated with occupational silica exposure (54, 55). Studies of silica and lupus nephritis are limited, but suggest little evidence of an effect (10, 56). Mechanisms leading to kidney disease and lupus nephritis may vary, however, and existing data cannot rule out silica-related effects in some subtypes. Occupational risk factors for cardiovascular disease, e.g., particulates (57, 58), have not been considered, but may be of interest given the increased cardiovascular risk in SLE patients.

Other research needs

A major limitation of the experimental literature on environmental factors and SLE (and other autoimmune diseases) is the lack of congruence between exposures studied in animal models and those identified as risk factors in human populations. New animal studies of silica may increase the plausibility of observational findings and help identify specific dose parameters, and susceptibility factors. Many substances can act as immune adjuvants; however, their effects on autoimmunity may depend on specific mechanisms, routes of exposure, clearance, patterns of tissue deposition, and timing of exposure relative to other

factors influencing an autoimmune reaction. In addition to silica and silicates, other potential adjuvants include mineral oils, endotoxins (e.g., in organic dusts), acrylates (e.g., in dental materials and other polymers), metals and nanoparticulates (e.g., from welding or new materials processes).

Overall, despite the challenges in studying SLE and industrial/occupational exposures, much progress has been made in the past decade identifying probable and possible exposures linked to increased SLE risk. The most fruitful approach for future studies of human SLE will require a strong emphasis on exposure assessment, specifically identifying individual products or chemicals (i.e., rather than studying broad groups such as solvents or pesticides) and more accurately quantifying dose. Studies in high risk populations (high exposure or high genetic risk) may offer the best chance of identifying the role of specific exposures linked to SLE.

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Table 1

Studies of occupational, industrial, and other chemical risk factors for SLE

Publications	Population/sample/design	Exposure assessment/ Analyses	Findings Odds Ratio or other effect measure (95% Confidence Interval)
Cooper et al., 2004(2); Parks et al., 2008(1)	US, North and South Carolina; Case-control 265 cases from rheumatology clinics and primary care 355 controls from driver's license registries, matched by age, sex, state	In person interview Questionnaire included lifetime job history of all jobs 1 year or longer, specific questions on jobs, tasks and materials, including silica, solvents; lifetime farm history (including pesticide mixing or application), crop/task-specific questions for dust, soil type mapping for silica Expert assessment occupational exposures: solvents Adjusted for matching factors, race, education	Pesticides (agricultural) – Mixing: OR=7.4 (1.4, 40) Applying: OR=0.77 (0.34, 1.8) Mercury – Exposure at work: OR=3.6 (1.3, 10) Dental worker: OR=7.1 (2.2, 23.4) Non-significant elevations ¹ : Hog or poultry processing (OR=1.6) Furniture or paper manufacture (OR=1.9) Beauticians (OR=1.6) No associations: occupational solvents Prior associations: silica (10)
Finckh et al., 2006(3)	US, Boston; Case-control 95 cases from community screening, hospital-databases 191 controls from community volunteers, matched by age and race	In person interview Questionnaire included lifetime job history of all jobs 1 year or longer, specific questions on jobs, tasks and materials, including silica, solvents Expert assessment: silica and solvents, using same protocol as Carolina Lupus Study (refs) Adjusted for parity, smoking, education	Silica – >1 year exposure: OR=4.3 (1.7, 11.2) No effect modification by smoking No association: occupational solvents
Gold et al., 2007(5)	US, 26 states; Case-control 7241 cases identified with ICD9 code for SLE on death certificate 264,569 controls who died without systemic autoimmune diseases	Usual occupation listed on the death certificate Job-exposure matrix (JEM) to assign exposures based on usual occupation Adjusted for age, sex, race, death year, US region, and socioeconomic status	Selected jobs with increased risk of SLE – Artists, performers, related: OR=2.90 (1.37, 6.15) Dental hygienists: OR=2.98 (1.14, 7.83) Farmers: OR=1.18 (0.95, 1.46) Mining machine operators: OR=1.77 (1.15, 2.73) Miscellaneous textile machine operators: OR=1.50 (1.05, 2.14) Hand painting, coating, decorating: OR=3.73 (1.31, 10.6) Garage/service station related: OR=2.26 (0.91, 5.63) Borderline association with JEM exposures – Solvents: OR=1.06 (0.99, 1.13) Pesticides (high vs. none): OR=1.07 (0.93, 1.22) No association with JEM exposures: asbestos, benzene, silica, inorganic dust, lead, metal dust, polycyclic aromatic hydrocarbons, wood dust
Cooper et al., 2010 (4)	Canada; Case-control 258 cases from rheumatology clinics, with at least 4 ACR criteria and 2 live parents (for DNA study); 90% female, 82% Caucasian 263 controls from random digit dialing, matched by age, sex, and area	Telephone interview Questionnaire on occupational exposures, based on job and task-specific questions: silica, gasoline, solvents, stains/varnishes, mercury, pesticides, hair dyes, permanents, relaxers, nail polish and application Adjusted for matching factors	Jobs/exposures – Artist (paints, dyes, film): OR=3.9 (1.3, 12.3) Nail polish or application: OR=10.2 (1.3, 81.5) Pottery/ceramics hobby: OR=3.9 (1.3, 12.3) Increasing risk across multiple sources of silica exposure (OR=1.00, 1.3, 2.1 for none, 1, and 2 or more, respectively, p<0.01 trend) Non-significant associations: occupational silica (OR 1.6), repairing/cleaning machinery or metal (OR 1.9), sterilizing dental

Publications	Population/sample/design	Exposure assessment/ Analyses	Findings Odds Ratio or other effect measure (95% Confidence Interval)
			equipment (OR=3.9), work with mercury 1+ time per week (OR=3.1) No associations: pesticides, gasoline exposure, hair dyes and permanents, drawing blood, stains/varnishes or paint strippers
Parks et al., 2011	US, Women's Health Initiative; Prospective cohort N=76,816 in cohort N=35 incident SLE cases in first 3 years of follow-up Cases identified by self-report and confirmed by DMARD status	Questionnaire – baseline, year 1 Residential and occupational application of insecticides, personal contact (mixed or applied) or application by others Adjusted for age, race/ethnicity, smoking, education, occupation, region, parity, ages of menarche and menopause, medical history (asthma, thyroid, other autoimmune disease)	Residential insecticide use – Trend for personal application p=0.06 Trend for application by others p=0.10 Combined analyses of RA and SLE: significant frequency and duration effects for personal use and stronger pesticide effect in women with a farm history, both for personal use and application by others
Li et al., 2012(6)	Sweden, case-cohort N=7.2 million males and 7.0 million females N=8,921 men and 42,290 women identified by ICD8, 9, and 10 for first hospital admissions with primary or secondary diagnosis of SLE Linkage of several national registries including total population census (1970, 1980) and hospital discharge registry (1964–2008)	Occupation listed in both 1970 and 1980 censuses, with at least 10 cases. Standardized incidence ratios for various occupational groups (with SLE incidence defined as first hospitalization) compared to the entire cohort	Men – Miners and quarry workers: SIR=6.0 (4.3, 8.3) Shoe and leather workers: SIR=6.9 (3.9, 11.5) Plumbers: SIR=2.2 (1.6, 2.9) Other construction workers: SIR=2.1 (1.7, 2.6) Glass, ceramics, tile workers: SIR=4.4 (3.5, 5.5) Chimney sweeps: SIR=4.5 (2.2, 8.5) Artistic workers: SIR=1.6 (1.3, 1.9) Electrical workers: SIR=1.6 (1.3, 1.9)

¹ Non-significant elevations (OR>1.5, p>0.05)