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# Epidemiology of Environmental Exposures and Human Autoimmune Diseases: Findings from a National Institute of Environmental Health Sciences Expert Panel Workshop

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## Abstract

Autoimmune diseases (AID) are a collection of many complex disorders of unknown etiology resulting in immune responses to self-antigens and are thought to result from interactions between genetic and environmental factors. Here we review the epidemiologic evidence for the role of environmental factors in the development of human AID, the conclusions that can be drawn from the existing data, critical knowledge gaps, and research needed to fill these gaps and to resolve uncertainties. We specifically summarize the state of knowledge and our levels of confidence in the role of specific agents in the development of autoimmune diseases, and we define the areas of greatest impact for future investigations. Among our consensus findings we are confident that: 1) crystalline silica exposure can contribute to the development of several AID; 2) solvent exposure can contribute to the development of systemic sclerosis; 3) smoking can contribute to the development of seropositive rheumatoid arthritis; and 4) an inverse association exists between ultraviolet radiation exposure and the risk of development of multiple sclerosis. We suggest that



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more studies of phenotypes, genotypes, and multiple exposures are needed. Additional knowledge gaps needing investigation include: defining important windows in the timing of exposures and latencies relating to age, developmental state, and hormonal changes; understanding dose-response relationships; and elucidating mechanisms for disease development. Addressing these essential issues will require more resources to support research, particularly of rare AID, but knowledge of the risks conferred by environmental factors in specific genetic contexts could pave the way for prevention of AID in the future.

**Keywords**

autoimmune disease; environmental risk factors; biologic agents; chemical agents; physical factors; research priorities

## 1. Introduction and Approaches

Autoimmune diseases (AID) are characterized by an inflammatory reaction caused by the body's own immune system attacking self-tissues. There are over 80 different AID, and collectively they are among the most prevalent diseases in the U.S., affecting at least 7% of the population. Because most AID are chronic and incurable, from a public health perspective they constitute a major health problem that, besides causing individual suffering, has high societal costs (Autoimmune Coordinating Committee report http://www.niaid.nih.gov/topics/autoimmune/Documents/adccfinal.pdf).

Our knowledge of the etiologies of AID is limited. Technological advances, increased funding, and coordinated international efforts have resulted in recent success in understanding the role of genetic risk factors for AID. Nonetheless, twin studies showing only low to moderate concordance rates, animal models, *in vitro* investigations, and case reports of subjects who develop an AID after exposure to an agent then improve after eliminating the agent and redevelop disease when exposed to the agent again, all suggest that the environment plays a substantial causative role in most of these diseases. Compared with the extent of genetic research, studies of environmental risk factors have received limited attention in many of these diseases. However, some areas of environmental research are relatively well developed, such as studies of the roles of silica and smoking in AID, as detailed below. The aims of the present article are to review what is known with regard to the epidemiology of the relationship between environmental exposures and AID and to prioritize topics for additional investigation.

For this review we focused on full peer-reviewed studies published within the last 30 years (search completed September 2010) in defined Medline searches using the terms under study and references in primary papers. We did not include in our search most therapeutic agents, vaccines, or medical devices. The diseases that we focused on were Crohn's disease (CD), gluten-sensitive enteropathy (GSE, celiac disease), Graves' disease (GD), Hashimoto's thyroiditis (HT), idiopathic inflammatory myopathies, multiple sclerosis (MS), primary biliary cirrhosis (PBC), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), type 1 diabetes (T1D), and ulcerative colitis (UC). We included other autoimmune diseases if there was a substantial literature for a certain environmental exposure. We included both risk factors and protective factors for the primary development of disease but not those relating to disease exacerbation or poor prognosis. Several meta-analyses of specific topics were included. We reviewed each meta-analysis with respect to study identification, inclusion and exclusion criteria, and the methods used to abstract and derive summary estimates. When the methods of the meta-analyses were viewed as acceptable by the group we used the summary estimate from the study as an

estimate of the evidence through the period covered by that review; additional studies of a given topic published after the meta-analysis were also identified and reviewed. Due to this journal's reference listing limitations, only the most recent or comprehensive references are cited when multiple studies support a finding. Readers can access a comprehensive list of references through September 2010 in the online supplement called Appendix 1.

We divided environmental exposures into three broad classes:

1. Chemical agents, including silica, asbestos, metals, pesticides, industrial chemicals and solvents, smoking, and personal care products (e.g., cosmetics and hair dyes),
2. Physical agents, including ionizing radiation, ultraviolet radiation (sunlight), and electric and magnetic fields
3. Biologic agents, including infectious agents, foods and dietary contaminants, molds, mycotoxins, and other toxins

We used the guidelines described in an evaluation of scientific studies relating to environmental contaminants and infertility (http://www.healthandenvironment.org/infertility/vallombrosa_documents) and the Hill guidelines to assess causality [1], to define levels of confidence of associations of exposures, and to make recommendations. The quality of the studies, particularly with respect to assessment of disease and assessment of exposure, was considered in evaluating variability in results among studies. For each class of exposures, two or three authors were primarily responsible for conducting the searches and abstracting data. The final classifications regarding the evidence were reached by consensus among all authors.

We summarize the evidence for specific associations between exposure and disease that we classified in the "confident," "likely," or "unlikely" categories regarding the contribution of the agent to the development of the disease. The "confident" category included exposure-disease associations in which support came from multiple studies from different populations using different designs (e.g., cohort, case-control); robust evidence of an overall association as identified by high-magnitude risks or the use of high-quality or established exposure assessment methods; evidence of an exposure-response gradient; and/or evidence of effect modification by disease subtype or genetics that supports biologic plausibility. The "likely" category included collections of research studies similar to those in the "confident" category but missing important elements, such as clarification of the temporal association between exposure and onset of an autoimmune disease, or they had less consistent results or were based on fewer studies. Associations were considered "unlikely" when a number of well-performed studies showed a lack of association. Associations were considered to have "insufficient" supporting data when no studies were reported or when the reported studies were too limited in design or power to allow conclusions to be drawn; those associations are not included in this review.

The epidemiologic studies pertaining to each of the exposure-disease associations in the "confident" category are presented in Table 1. A summary of the relations we classified as either "confident" or "likely" and their research priorities are presented in Table 2. The supporting data are discussed below.

## 2. Chemical Factors

### 2.1 Silica

This field of research began with the initial description of SSc among Scottish stonemasons in 1914 [2] and became more fully developed through studies of miners and granite workers in the 1950s through 1980s. Freshly fractured particulate silica (crystalline silica or quartz)

is released typically in mining but also in the so-called dusty trades, including sandblasting, rock drilling, sand factory work, granite cutting, construction work, brick laying, tilling, and cement work. Variable levels of agricultural exposures are also likely depending on the silica component in soil Animal and basic science studies support a role for silica as a T-cell adjuvant and possible trigger of autoimmunity (see accompanying animal model paper).

A 2002 meta-analysis summarized the epidemiologic studies investigating the association between exposure to crystalline silica from a variety of sources and the risk of developing RA [3]. Two case-control studies, two proportionate mortality studies, and six cohort studies performed between 1986 and 2001 were included, with a total sample size of 242 exposed cases. Nine of the ten studies had reported elevated risk of developing RA associated with exposure to crystalline silica from a variety of sources. Overall the summary relative risk (RR) for all studies indicated that disease risk for exposed individuals was more than three times that of unexposed individuals (3.43, 95%CI 2.25-5.22), and the risk appeared to be higher in males, possibly because of increased levels of job-related exposure [3]. When the cohort studies alone were examined, the RR of RA associated with silica exposure was 4.5. Several of the studies showed a dose response with increased risk at higher level of exposure. Since publication of that meta-analysis, data from an RA inception cohort study in Sweden reported that men in highly exposed occupations had a three-fold higher risk of developing RA [4]. This risk was specifically for anti-citrullinated protein/peptide antibody (ACPA)-positive RA but not ACPA-negative RA, and a strong interaction with cigarette smoking was also seen. The risk for ACPA-positive RA among silica-exposed current smokers was 7.4 times higher than among non-smokers without silica exposure, exceeding the risk expected from the separate effects of silica and smoking, with an attributable proportion due to the interaction of 60% [5].

Several studies have investigated the role of silica exposure in SSc, a disease that is much less common than RA. A recent meta-analysis summarized three cohort, nine case-control, one case series, and three mortality studies from a variety of sources and reported a summary estimate of 3.2 times higher risk of SSc associated with silica exposure [6]. The risk was elevated only among males and not among females. The relative risks observed in the three cohort studies, perhaps because of higher levels of exposures, were extremely high, with over 15-fold higher risks.

Epidemiologic data provide convincing evidence of the contribution of silica exposure to the development of SLE, with three population-based, case-control studies of SLE from the southeastern United States [7], Boston [8], and Canada [9]. The exposure assessment methodology was similar in these three studies (detailed occupational history collected by a trained interviewer, with exposure assessed by investigators blinded to case-control status), but the sources of exposure differed. These studies provide evidence of higher risk with higher exposure. However, one case-control study involving 51 cases with biopsy-confirmed SLE nephritis compared to 51 age-, race-, and sex-matched control subjects with other renal diseases did not find an association with silica dust exposure [10].

Several case-control studies from Europe [11-13] and the United States [10, 14] support the association between crystalline silica exposure and increased risk of anti-neutrophil cytoplasmic antibody (ANCA)-related diseases, including ANCA positivity, ANCA-positive small vessel vasculitis (with pulmonary involvement) [13], or biopsy-confirmed glomerulonephritis [10, 14]. The RR associated with silica exposure was greater than 2.0 compared with non-exposed individuals in almost all studies, and a dose effect was reported in one study [14]. Nonetheless, a recent large case-control study from Sweden did not find a significant assocation of Wegener’s granulomatosis with 32 occupations evaluated [15].

The associations between silica exposure and other AID have not been adequately examined, but the available data indicate that this could be a useful avenue for future research, for example, with respect to sarcoidosis.

### 2.2 Asbestos

Based on current published data, we believe that there is insufficient evidence that exposure to asbestos plays a causative role in the development of any AID. Asbestos is another silicate that occurs in mining and construction but historically has occurred in a variety of other industries. In many settings, because asbestos exposure often is concurrent with crystalline silica exposure, it is difficult to assess the role of each material separately. Asbestos inhalation is strongly associated with lung cancer, mesothelioma, and pulmonary asbestosis. Limited epidemiologic data indicate that asbestos might contribute to development of RA [16]. This evidence includes a case-control study in a population of workers and community members exposed to asbestos-contaminated vermiculite in Libby, Montana, in which multiple pathways of exposure to asbestos, at home and on the job, were assessed [17]. Classification of connective tissue diseases was based on self-report, with confirmation from a repeat of the self-reported diagnosis in a subsequent interview; thus no medical records were evaluated to confirm the diagnosis. For risk of RA, an association with asbestos exposure was observed only among individuals over age 65. A dose response was seen in that higher risk was associated with a greater number of exposure pathways (i.e., work, home). When RA, SLE, and SSc were combined, the related risk was 2.14 (95% CI 0.90, 5.10) for any single exposure pathway and up to 4.45 for four or more pathways of exposure. A case-control study in Sweden involving 74 men with newly diagnosed RA and 382 controls found an association with occupational asbestos exposure, OR 2.5 (95% CI 1.0-6.8), after adjustment for age and smoking history [18].

In addition, several studies of varying quality have reported asbestos exposure to be associated with immune activation or autoimmunity (e.g., elevated immunoglobulins or rheumatoid factor, anti-nuclear antibody (ANA), and ANCA) in the absence of confirmed AID [19, 20]. These studies are limited by use of older immune assay techniques, small sample sizes, and lack of adequate controls and statistical analyses. Three small case-control studies investigated risk of ANCA-positive small vessel vasculitis associated with asbestos exposure, two of which reported an elevated risk [13].

### 2.3 Metals

Based on current published data, we believe that there is insufficient evidence to show that exposure to metals plays a causative role in the development of any AID. However, rodent models of mercury-induced autoimmunity suggest that it is biologically plausible that some heavy metals could act as antigens in AID pathogenesis. With the exception of several epidemiologic studies investigating the role of mercury amalgam fillings in MS, few studies have investigated the potential role of metal exposures as antecedents to AID.

Aminzadeh et al. [21] performed a meta-analysis of four studies that examined the relation between exposure to mercury amalgam dental fillings and the risk of developing MS. The meta-analytic summary odds ratio was 1.2 (95% CI 0.96-1.61), and significant heterogeneity existed among the effect estimates. Furthermore, several studies failed to demonstrate any significant dose-response trends between number of amalgam fillings (or duration of exposure) and risk of MS [22, 23].

For other AID, there are too few studies of environmental or occupational metal exposures to draw firm conclusions. Mercury-exposed gold miners in Brazil were found to have significantly higher anti-nuclear and anti-nucleolar antibodies compared to non-mercury-

using miners of diamonds and emeralds; however, neither symptoms nor AID status was assessed [24]. To date, only one group investigated the possible role of occupational and avocational metal exposures in SLE [9]. Exposure to mercury in the occupational setting at least once per week was associated with a modestly (but not significantly) higher risk of SLE (OR 3.1; 95% CI 0.8-12.7). Exposure to five or more days of stained or leaded glass as a hobby was also more common among SLE cases than controls, but again, the rarity of the exposure led to an imprecise effect estimate (OR 3.0; 95% CI 0.8-11.6).

### 2.4 Pesticides and persistent organic pollutants

Based on current published data, we believe that there is insufficient evidence that exposure to pesticides or persistent organic pollutants play a causative role in the development of any AID. Nonetheless, pesticides have long been suspected risk factors for AID because epidemiologic studies reported higher risks for RA and SLE among farmers [25]. In two studies, occupational pesticide exposure was associated with 20-30% non-significantly higher risk of RA in men [26, 27]; however, other studies have did not find an association [18, 28]. A history of mixing pesticides for agricultural work was associated with development of SLE (although only 8% of SLE cases and 1% of controls reported the exposure) [29], but pesticide application was not associated with SLE in the same study. In a recent analysis of the Women's Health Initiative cohort, 50- to 79-year-old women who reported personally mixing/applying insecticides (mostly in a residential setting) had higher risks of developing RA and SLE during the study follow-up, with trends of increasing risk by frequency and duration of use [30]. A history of living on a farm was also associated with higher risks of RA and SLE [30]. It is possible that pesticides contribute to increased risk of rheumatic autoimmune diseases such as RA and SLE; however, inference from the existing data is limited in terms of biologic mechanisms or intervention strategies because no specific pesticides have been identified as potential causal agents. More research is needed to clarify risks associated with specific pesticide agents–exposures that often exist in the context of mixtures and multiple exposures.

Persistent organic pollutants (POPs) are halogenated organic compounds that are resistant to environmental degradation through chemical, biological, or photolytic processes. POPs include broad classes of compounds, such as organochlorine pesticides (and pesticide metabolites), polychlorinated biphenyls (PCBs), dioxins, and furans. The POPs that have been studied most extensively are PCBs, but often exposure is to a mixture of compounds that are not specifically measured.

There have been few epidemiologic studies of POPs in relation to AID. One study of U.S. electrical workers (typically exposed to PCBs) reported 30% significantly more mortality from musculoskeletal system diseases (ICD-9 codes 710-739) and 40% more mortality from arthritis and spondylitis (ICD-9 codes 710-725, classifications that include the ICD-9 codes for RA and SLE) [31]. One cohort study with 24 years of follow-up in a Taiwanese population that was accidentally exposed to high levels of PCBs and furans through consumption of contaminated rice found much higher mortality from SLE, with PCB-related deaths starting 10 years after the exposure [32]. In the 1999-2002 National Health and Nutrition Examination Survey (NHANES) [33], serum was used to measure POPs, including dioxins, furans, PCBs, and organochlorine pesticides, among 1721 adults aged 20 years and older. Serum PCB concentrations were strongly associated with self-reported prevalent RA in women, although self-reported RA is less accurate than physician-reported RA. The risk estimates for RA (N=93 RA cases) were higher in higher quartiles of women exposed to non-dioxin-like PCBs; compared to the lowest quartile, the risk for the 2$^{nd}$ quartile was 2.2 (95% CI=0.6-7.4), 4.4 for the 3$^{rd}$ quartile (95% CI=1.3-15.2), and 5.4 for the 4$^{th}$ quartile (95% CI=1.4-20.3). The summed concentration of all organochlorine pesticides was also modestly associated with RA (highest versus lowest quartile: OR=3.5, 95% CI=0.9-14.0),

and the pesticide metabolite oxychlordane showed a particularly strong association. Notably, dioxins and furans were not associated with RA. Although it is possible that POPs increase the risk of RA and/or SLE, more studies investigating the association are needed.

There is some evidence that exposure to PCBs contributes to the development of anti-thyroid antibodies. Although many studies of POPs and thyroid health did not measure thyroid autoantibody levels, the ones that did typically found elevated autoantibodies to thyroperoxidase (ATPO) and/or thyroglobulin (ATG) among persons with higher blood concentration of PCBs or organochlorine pesticides (p,p'-DDE) [34, 35]. Many POPs are structurally similar to thyroid hormone and thus might interfere with hormone binding [34]. Nevertheless, it is unclear whether the presence of thyroid autoantibodies has immediate clinical significance.

### 2.5 Solvents and other industrial chemicals

Research in this area began in the 1950s after case reports of patients who developed a scleroderma-like syndrome after exposure to vinyl chloride, epoxy resins, trichloroethylene, perchloroethylene, or mixed solvents. Although not all of these industrial chemicals are solvents, per se, some, like vinyl chloride, share structural similarities with chlorinated solvents, and others, like epoxy resins, can contain solvent mixtures.

Many epidemiologic studies have investigated whether an association exists between solvent exposure and increased risk of SSc, the majority with positive results. Relevant epidemiologic data were synthesized in a meta-analysis published in 2007 [36], which included 11 epidemiologic studies consisting of 1291 cases and 3435 controls. The meta-analytic risk estimate for occupational exposure to solvents (ever vs. never) was 2.4 (95% CI 1.7-3.4). The risk of SSc associated with solvent exposure was significantly higher in both men and women, with a notably higher risk estimate for men (men RR = 3.0, 95% CI 1.9-4.6; women RR = 1.8, 95% CI 1.5-2.1). A higher RR for men may reflect lower baseline risk of SSc, higher occupational exposure to solvent, or greater susceptibility to solvent exposure. The overall summary risk estimate remained statistically significant after adjustment for publication bias. Two studies that assessed the degree of exposure reported higher RR estimates for high cumulative exposure scores than for low exposure or ever exposed [37, 38].

Several studies have collected detailed data to examine which specific solvents account for the association between solvents and risk of SSc [37-39]. These studies generally reported elevated risks associated with many of the specific solvents examined, including toluene, xylene, and trichloroethylene, and with broad solvent categories, such as chlorinated solvents and paint thinners and removers. In a large case-control study (660 cases, 2227 controls), limited to women, the risk of SSc increased with duration of exposure to any solvent, but duration did not matter for specific solvent exposures [39]. In a meta-analysis, three studies that reported risk estimates for occupational trichloroethylene exposure [37-39] were combined to obtain a risk estimate of 2.5 (95% CI 1.1-5.4) for men and 1.2 (95% CI 0.6-2.6 for women) [40].

A potential association between solvent exposure and increased risk of MS has also been investigated. An analysis of three cohorts of workers defined on the basis of 1970 census records in Norway found a two-fold higher risk among painters compared with a group of workers not exposed to paint or solvents (e.g., construction workers, food service workers) (RR 2.0, 95% CI 0.9-4.5) [41]. Although positive associations between solvent exposure and MS were also found in some case-control studies conducted in the 1970s and 1980s [42], the exposure assessment methodologies used in those studies were not rigorous.

Data on the possible role of solvents in causing other AID are insufficient, with a few studies reporting mixed results for RA [26, 27] and SLE [8, 9, 29].

There has been much less research on other industrial chemicals in relation to AID. The existing studies are limited to a few diseases; therefore, we believe there is insufficient evidence that exposure to other industrial chemicals plays a causative role in the development of AID. One study found 2.5-fold higher risk of SSc associated with any combination of vinyl chloride, epoxy resins, or formaldehyde (OR 2.5, 95% CI 0.8-8.0) that was statistically significant among men (OR 18.6, 95% CI 1.4-251) [43]. Other studies found associations between SSc and epoxy resin [37], synthetic adhesives [44], and welding fumes [37].

There has been virtually no epidemiologic research on risks associated with relatively widespread synthetic chemical exposures, such as plasticizers (e.g., phthalates and bisphenol A). Some of these chemicals can act as endocrine or immune disruptors, and increased risks of some immune-mediated diseases, including asthma and eczema, in relation to exposure levels, have been reported in children [45]. More research is needed to determine the role of plasticizers and other industrial chemicals in consumer products in the development of AID.

### 2.6 Smoking

Numerous case-control and cohort studies have demonstrated higher risk for the development of RA in relation to smoking history, with a higher risk in rheumatoid factor (RF)-positive or ACPA-positive RA. A gene-environment interaction with the human leukocyte antigen (HLA) shared epitope (SE) has also been demonstrated in studies from Sweden, Korea, and the United States [46-48]. There appears to be a higher risk associated with greater exposure, in particular, after 10 pack-years of smoking in women, and the risk of RA remains elevated for up to 20 years after smoking cessation [49]. Additional support for the role of smoking in RA comes from animal models, laboratory investigations, and clinical studies [50].

There have been fewer investigations of smoking in relation to other AID, including MS, GD, HT, SLE, CD, and UC. Studies supporting smoking as a risk factor for this diverse group of AID include cohort investigations of large populations as well as many case-control studies [51, 52]. Data supporting the association between MS and smoking come from case-control and longitudinal investigations, although not all studies have shown positive associations [53]. A meta-analysis of smoking and SLE found a pooled RR estimate for ever (vs. never) smoked of 1.5 (95%CI 1.09-2.08), but for past smokers the risk was not elevated (1.0, 95%CI 0.75-1.27) [54]. A meta-analysis of the studies of smoking and thyroid disease suggests that current smoking results in higher risk for both GD and HT [55]. Cigarette smoking has been reported as a risk factor for Graves' ophthalmopathy in particular [55]. The relationship between smoking and inflammatory bowel disease is complex in that it is likely that current smoking contributes to the development of CD but is protective for the development of UC [56, 57].

### 2.7 Hair dyes and cosmetic products

Based on current published data, we believe that there is insufficient evidence that exposure to cosmetic products plays a causative role in the development of any AID. Exposure to chemical agents in hair products or cosmetics is very common among women; therefore, if one or more of such exposures contributes to AID risk, such a finding would have important public health significance. Thus, these agents merit further investigation in epidemiologic studies of AID.

The rationale for investigating hair dyes in SLE was based on the observation that certain drugs containing aromatic amines (procainamide, sulfadiazine, hydralazine, and isoniazid) can induce a reversible lupus-like syndrome. That observation led to early speculation that exposure to permanent hair dyes containing aromatic amines could be a risk factor for SLE; however, the most carefully conducted epidemiologic studies have failed to identify an association between hair dyes and SLE [9, 58]. A recent investigation [9] found an association between employment involving nail polish or nail applications and risk of SLE (OR 10.2; 95% CI 1.3, 81.5), an interesting finding that merits replication. Other AID for which hair dyes or cosmetic products have been investigated are PBC and RA. The use of hair dyes was significantly associated with a higher risk of PBC in a study conducted in the United Kingdom [59]. In a U.S. study, nail polish use was significantly more frequent among women with PBC than among control women [60]. The single case-control study of RA found that women who were occupationally exposed to hairdressing chemicals were at greater risk than unexposed women for developing RA (OR 3.0; 95% CI 1.0-9.4) [27].

## 3. Physical Factors

### 3.1 Ionizing radiation

The thyroid is a target organ for radiation-related damage in that ionizing radiation is a known cause of thyroid cancer; therefore, other thyroid abnormalities have also been assessed as potential outcomes of exposure. There is convincing evidence that external radiation treatment for cancer increases the risk of autoimmune thyroiditis and GD, especially in treatment for cancers of the neck region (e.g., Hodgkin disease, thyroid cancer, head and neck cancers) [61, 62]. Radioiodine therapy for nodular toxic goiter or toxic adenoma can cause GD [63]. Overt hypothyroidism occurs in about 20-30% of patients treated with radiotherapy, and the effect is dose dependent. One study showed that almost all patients administered a dose above 40 Gray (Gy) to the thyroid gland developed a significant increase in thyroid-stimulating hormone level [62]. Nevertheless, most studies that followed cohorts of treated patients did not differentiate HT from general hypothyroidism.

One study examined almost 2500 persons exposed primarily to radioiodine between age 12 and 18 years in communities near the Nevada nuclear weapons test site (Nevada Test Site). These subjects were evaluated up to 30 years after exposure [64]. The total estimated absorbed dose to the thyroid was associated with development of thyroiditis in a dose-dependent manner, with a 5.6-fold higher risk of thyroiditis associated with a dose ≥410 mGy (compared to ≤74 mGy). However, other studies (using different exposure assessment methods) of residents in the fallout area from the Nevada Test Site [65] and near the Hanford nuclear site in Washington State [66] found no association between the total estimated ionizing radiation dose and risk of thyroiditis.

Studies of Chernobyl-contaminated regions have found increased prevalence and/or levels of anti-thyroid antibodies (ATPO, ATG, or anti-thyroid microsomal autoantibodies) in persons exposed during infancy or childhood, when assessed 5 to 15 years after the accident [67, 68]. Despite elevated autoantibodies, the prevalence of thyroiditis has generally not been associated with exposure in those studies. Most of the studies compared Chernobyl-contaminated to uncontaminated regions, without evaluating radiation dose, per se, and therefore might have missed specific dose-response relationships. One study, conducted in a Ukrainian population, compared thyroid disease outcomes to the $^{131}$I thyroid dose among persons less than 18 years old at the time of the Chernobyl accident [68]. In clinical examinations conducted 12 to 14 years later, $^{131}$I dose was significantly associated with elevated ATPO (>60 U/mL), with a 40% higher risk in the highest dose category. There were significant associations between the thyroid radiation dose and autoimmune thyroiditis

in men but not women; the dose-response relationship in men also followed a nonlinear, concave pattern.

Other AID have not been well studied in relation to ionizing radiation exposure. A pooled analysis of two case-control studies of MS conducted in Sweden reported that occupational exposure to ionizing radiation (e.g., in hospitals or industry) was associated with over four-fold higher risk of MS (OR 4.4, 95% CI 1.6-11.6) [69]. Receiving frequent X-ray examinations was also associated with higher risk of MS, with an odds ratio of 1.8 (95% CI 1.2-2.6).

### 3.2 Ultraviolet radiation

One of the most striking trends in geographically based epidemiologic studies is the strong gradient in the prevalence of MS that is observed in relation to distance from the equator [70]. Although viral agent(s) or other climactic factors might be partly responsible for this gradient, the most important contributor is likely to be effects from the ultraviolet radiation (UVR) in sun exposure [71]. A strong and consistent inverse association has been observed in study designs of several types (ecologic studies, twin studies, and cohort and case-control studies); almost all have shown an association between greater sunlight exposure and reduced risk of MS [53]. The strength of the observed associations was generally high, and the inverse association with sunlight persisted even after controlling for socioeconomic status, birthplace, skin color, and other covariates. Furthermore, several studies that have used objective measures of sun exposure, such as actinic skin damage measures or spectrophotometric skin type, have also found significant inverse associations between these measures and disease risk [72]. Two studies have reported that the inverse association between sunlight exposure and MS was significantly attenuated (and no longer statistically significant) after adjusting for latitude [73, 74]; however, latitude and sunlight exposure are highly correlated, and disentangling their effects is challenging.

Some observations suggest that sunlight exposure early in life (before puberty or age 15) is important with respect to the influence of sunlight on risk of MS. Several epidemiologic studies collected information on early-life exposure to UVR and have shown a significant inverse association of MS risk with sunburn at 1 year of age [74], with 2-3 hours of weekly peak sun exposure prior to age 15 [72], and with time spent in summer outdoor activities prior to 20 years of age [75]. Individuals who migrate from a high-risk (high latitude-low sunshine) area prior to age 15 acquire the lower risk of the latitude to which they migrate, whereas individuals who migrate from a high-risk area after puberty retain the higher risk of the latitude from which they migrated [53].

Several studies have found inverse associations between ecologic measures of UVB irradiance and/or latitude and incidence of T1D [76, 77], RA [78], and autoimmune vasculitides [79]. UVR in the B wavelengths, adjusted for cloud cover, was significantly associated with incidence of T1D in a study combining data from 51 regions worldwide [76]. In a meta-analysis of case-control studies from 19 regions (Europe, South America, and Asia) that analyzed vitamin D receptor polymorphisms in relation to T1D, the inclusion of winter UVR level as a covariate substantially reduced the observed between-study heterogeneity for Fok1, Bsm1, and Taq1 polymorphisms [80]. These intriguing data on sunlight as a possible preventive factor for T1D and certain other AID should be followed up in population-based, individual-level studies in which sunlight exposure data are based on personal activity information (time spent outdoors in work and leisure at different ages and use of sun screens or protective clothing) in addition to ecologic data (latitude, UV irradiance).

In contrast to the suggested protective effect of sunlight for several AID, described above, limited data suggest that exposure to sunlight might be a risk factor for SLE. SLE risk has been associated with outdoor work in the year before diagnosis (OR 1.9, 95% CI 1.0-3.7), particularly among those who are prone to sunburn [9] and among persons who had serious sunburns before age 20 (OR 2.2, 95% CI 1.2-4.1) [81]. Although these scant data on sunlight exposure in relation to higher risk of SLE are intriguing, they might partially reflect sun sensitivity resulting from early SLE symptoms; therefore, replication of the associations should be pursued in prospective cohort studies in which sun exposure information is collected before disease onset.

UVR has also been anecdotally associated with the onset and increased disease activity in dermatomyositis, a form of idiopathic inflammatory myopathy [82]. Both international [83] and U.S. [84] studies have reported associations of the extent of UVR at the location of disease onset with the relative frequency of dermatomyositis versus polymyositis (a disease without photosensitive rashes) in the study populations. These results warrant additional research in this area.

## 4. Biologic agents

### 4.1 Infections

The concept that infections play a role in the development of AID has a long history, and many infectious agents, including viruses, bacteria, and parasites, have been proposed as triggers for particular AID. A common pattern, however, is that after initial positive reports, subsequent studies have not been able to reproduce the initial finding.

The database of epidemiologic studies of Epstein-Barr virus (EBV) and MS is relatively strong [85] such that, in aggregate, the data support the contention that EBV infection likely contributes to the development of MS. Multiple lines of evidence include a) studies showing associations of MS with molecular and antibody markers of EBV [86], b) studies showing associations of prior infectious mononucleosis with MS, and c) evidence that HLA DRB1*1501-positive individuals are more vulnerable to EBV-associated MS [87]. A dose-response effect has been demonstrated in that higher anti-EBV nuclear antigen antibody titers have stronger associations with MS [88]. Furthermore, prospective studies suggest that MS risk is extremely low in individuals who are EBV negative, but risk increases several fold after EBV infection [89]. Less convincing data exist for the role of EBV in development of other AID, but it is possible that EBV might initiate SLE or RA [90-93].

Other infections have been studied less than EBV, but it is possible that parvovirus B19 contributes to the development of RA. One study demonstrated associations between viral DNA and anti-viral antibodies in plasma, synovial fluid, and synovial tissue [94]. Enteroviruses might contribute to the development of T1D. Viral RNA and antibodies have been associated with T1D, with development of islet cell and glutamic acid decarboxylase autoantibodies [95, 96], and prospective studies suggested that the risk of T1D is higher after detection of enteroviral RNA in serum [97, 98].

### 4.2 Diet, foods, and dietary contaminants

When considering dietary factors in AID, the gold standard is the causation of GSE by ingesting gluten. Epidemiological studies of the association between gluten and GSE are not included in Table 1 because this association was established years ago and is well documented in the scientific literature via dose-response, laboratory, ecologic, and case data showing that gluten ingestion causes GSE, also known as celiac disease [99, 100]. There are no other associations between dietary factors and autoimmune disease for which we have this level of confidence. However, it is still not known why some individuals with the

genetic risk factors develop GSE and others do not, given that most if not all are exposed to gluten. With regard to other dietary agents, we are confident of the well-documented outbreaks of toxic oil syndrome as a result of ingesting contaminated rapeseed oil [101], as well as the association of eosinophilia-myalgia syndrome to certain supplements containing L-tryptophan [102].

For several dietary factors, we consider the associations that are likely but in need of confirmation. For example, much research has been done on the links between breast-feeding and the age at which certain foods are introduced into the infant's diet (e.g., milk, cereals, etc.) and development of T1D or GSE. The associations between early introduction of complex foods and the development of T1D or GSE were initially detected in numerous case-control studies [103, 104]. Subsequent cohort studies using disease-specific autoantibodies as the outcome [105-108] have provided additional support for these associations. However, these findings are not consistent with regard to the type of antigen that is important (in some cases it is cow's milk, in others it is cereal or gluten, and in yet others it is fruits or root vegetables). Additionally, an observed effect of removing all intact protein (i.e., the pilot hydrolyzed protein formula intervention) [109] on decreased likelihood of T1D does not definitively demonstrate which antigen is important but simply that one can manipulate the immune system by removing intact proteins from the infant's diet. These findings suggest a relationship between exposure to complex foods early in infancy and development of AID that is not necessarily antigen specific but perhaps more based on the order in which foods are introduced to the diet and other factors.

The association between low vitamin D intake or level and MS is interesting because, for several years, this association had been widely accepted without strong epidemiological evidence. Only recently have there been two prospective studies, one examining intake [110] and one examining vitamin D blood levels [111] that have provided compelling evidence for this hypothesis. The data linking higher levels of UVR exposure, potentially via vitamin D generation in the skin, to lower MS susceptibility are also strong (see Section 3.2). Although this association is likely, additional studies are still needed to investigate this association in other ethnic or racial groups and to explore a dose effect. Although case-control studies have shown associations between vitamin D levels and existent SLE, RA, and other AID, no associations were found between dietary intake of vitamin D and future risk of developing either RA or SLE among the women followed in the Nurses' Health Study cohort. Very little prospective evidence exists for an association between dietary vitamin D intake and risk of developing any other AID.

We consider several associations between diet and AID to have insufficient supporting data because they show inconsistent results or consistent results in only one type of study design (e.g., case-control studies) or because the findings have not been replicated. These unclear associations include 1) low antioxidant vitamin intake and increased risk of RA [112], which was not replicated in RA or SLE in the much larger prospective Nurses' Health Study, which prospectively collected dietary exposures and followed up subjects for 22 years [113]; 2) low fruit or fiber intake and CD or UC [114-116]; 3) high sweets or fat intake and CD or UC [114, 117, 118]; 4) current cow's milk consumption and T1D [119, 120]; 5) low alcohol consumption and RA [121-123]; and 6) high coffee intake and RA [122, 124, 125], which was not confirmed in the Nurses' Health Study [126].

Other foods or chemicals in food or dietary supplements have been reported to be associated with risk of a variety of diseases, although the data are limited and therefore are considered insufficient. For example, there have been only case reports and animal studies linking tartrazine [127, 128] and L-canavanine [129-131] to the induction of autoimmunity. However, a Swedish case-control study found that ingestion of alfalfa sprouts (which

contain L-canavanine) was not associated with SLE risk [81]. Additional epidemiologic studies investigating associations of food chemicals, dyes, or additives with risk of developing AID are needed.

Associations between nitrates, nitrites, and nitrosamines and increased risk of T1D have been observed in several studies [132, 133]; however, because no prospective studies have examined them, there are insufficient data to support an association.

## 5. Summary of assessments of confident and likely associations between environmental agents and autoimmune diseases

### 5.1 Based on existing evidence we are confident of the following

#### 5.1.1 Chemical factors

1. Crystalline silica exposure contributes to the development of several AID, including RA, SSc, SLE, and ANCA-related vasculitis.
2. Solvent exposure contributes to the development SSc.
3. Smoking contributes to the development of ACPA-positive and anti-RF-positive RA, and there is an interaction with the shared epitope.

#### 5.1.2 Physical factors

1. An inverse association exists between higher UVR exposure and lower risk of development of MS.

#### 5.1.3 Biological factors

1. Ingestion of gluten contributes to the development of GSE.
2. Ingestion of certain lots of L-tryptophan contributes to the development of eosinophilia-myalgia syndrome.
3. Dietary intake of 1,2-di-oleyl ester (DEPAP)- and oleic anilide-contaminated rapeseed oil contributes to the development of toxic oil syndrome.

### 5.2 Based on existing evidence we consider the following likely but requiring confirmation

#### 5.2.1 Chemical factors

1. Solvents contribute to the development of MS.
2. Smoking contributes to the development of seronegative RA, MS, SLE, HT, GD, and CD.
3. Current smoking protects from the development of UC.

#### 5.2.2 Physical factors

1. Ionizing radiation contributes to the development of HT and GD.

#### 5.2.3 Biological factors

1. EBV infection contributes to the development of MS.
2. Early introduction of complex foods contributes to development of T1D and GSE.
3. Low vitamin D dietary intake and blood level contribute to development of MS.

### 5.3 Based on existing evidence we consider the following factors unlikely to contribute to the AID listed

1. Hair dye use does not contribute to the development of SLE.

## 6. Discussion

Many recent advances have helped to decipher the factors that contribute to the development of AID. The development of efficient and reliable high-throughput genotyping techniques has resulted in many studies designed to discover genetic risk factors for AID. Frequent findings from these studies are strong associations with different alleles of genes within the HLA region, and multiple, weaker associations with non-major histocompatibility genes. Several years into the era of genome-wide association studies, however, even the combined effect of all the identified genetic risk factors does not fully explain the incidence of these diseases, and the evidence is increasing that the roles of environmental agents are critical components that need to be understood to elucidate causes of AID [134, 135]. Just as multiple genetic risk factors are important in the development of a given AID, it is likely that multiple environmental risk factors may need to be present at different periods of life, or in a specific temporal sequence, to induce the immune perturbations that result in AID [136]. It is also likely that there are many ways or mechanisms by which similar clinical AID phenotypes develop (see the accompanying paper on mechanisms for the development of AID) and that a given AID could have multiple environmental risk factors, and in turn, that certain environmental agents could be risk factors for multiple AID.

The many difficulties inherent in investigating environmental risk factors are a major limitation in making progress in this area, including the difficulty of obtaining high-quality exposure data using validated methods, the likelihood of there being different environmental effects during different time windows in growth and development, difficulties in defining which of the many concurrent environmental exposures are related to disease, inadequate training in environmental medicine and inadequate interdisciplinary research and collaboration between clinicians and epidemiologists, and the need for greater resources to address these issues in the future. Additional challenges, which are not unique to studying environmental risk factors, include the relative rarity of specific AID, which results in small numbers of cases and limited statistical power in prospective cohort studies, and the lack of standardized registries for AID to facilitate systematic case identification for epidemiologic research.

While many environmental factors have been suggested as being related to the pathogenesis of AID, common themes of our evaluation indicate that additional progress—by focused and coordinated efforts—is needed in particular areas. For example, the role of multiple exposures and conversely the identification of single causal agents within groups of exposures (e.g., specific solvents or pesticides contributing to increased risk for the group) need to be investigated. More studies of environmental exposure risks within AID phenotypes and in the context of risk genotypes are needed to elucidate associations that might be specific, such as the apparent differing smoking risks for RA according to RF or ACPA positivity. Additionally, it is necessary to define critical windows in the timing of exposures and latencies relating to age, developmental state, and hormonal changes, to understand dose-response relationships and to elucidate mechanisms for disease development.

In summary, we have conducted a comprehensive review of the current literature using predetermined criteria to assess the levels of confidence for the association of environmental agents with multiple AID, with the added objective of defining high-priority research areas. There is obviously an extensive body of literature and space does not permit all relevant

citations. We do note a recent symposia and dedicated issues as part of the Congress of Autoimmunity on this theme [146-187]. Based on the above data and the approaches outlined, we are confident that several environmental exposures contribute to the development of AID (Table 1) and that there is sufficient evidence that other exposures likely contribute to the development of AID (Table 2). Finally, we recommend specific research areas to be pursued based on the strength of the current data and the public health impact (Table 2).

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## Table 1

Environmental Exposures that We Are Confident Contribute to the Development of Human Autoimmune Disease

| Exposure/Disease association/Assessment method(s) | Study Designs | Results: Risk Ratio (95% CI) | Comments | References |
|---|---|---|---|---|
| **Silica and RA** | | | | |
| Occupational exposure (structured interviews and questionnaires) | Meta-analysis of 10 studies from Europe, South Africa, and United States (total 242 cases), published 1986–2001; one subsequent cohort and two subsequent case-control studies | From meta-analysis (2 case-control, 2 proportionate mortality, and 6 cohort studies):<br>all studies: 3.43 (2.25–5.22)<br>males: 4.45 (2.24–8.86)<br>cohorts: 4.53 (2.94–7.00) | Individual RR estimates from 0.79 to 8.3; 8 of 10 RR estimates between 2 and 8. In one study, interaction with smoking: Smokers: 7.36 (3.31–16.38); one study, higher risk in ACPA+ compared with ACPA- | [3-5, 137] |
| **Silica and SSc** | | | | |
| Occupational exposure (structured interviews and questionnaire) | Meta-analysis of 16 studies from Europe, Australia, and United States (total 1,101 cases), published 1967–2007 | From meta-analysis (3 cohort, 9 case-control, 3 mortality):<br>all studies: 3.20 (1.89–5.43)<br>females: 1.03 (0.74–1.44)<br>males: 3.02 (1.24–7.35)<br>cohort: 15.49 (4.54–52.87)<br>case-control: 2.24 (1.65–3.31) | Individual RR estimates from 0.87 to 37; 11 of 16 RR estimates ≥ 1.5 (interquartile range 1.4 to 5.6) | [6, 137] |
| **Silica and SLE** | | | | |
| Occupational exposure (structured interviews) | 3 case-control and 3 cohort studies from Europe and North America (total 659 cases) | Positive associations seen in each of the studies: case-control (general population) RR estimates ranged from 1.6 (any exposure) to 4.9 (high exposure); RR > 10 in highly exposed populations (i.e., people with silicosis) | Exposure-response pattern seen within and among studies | [7-9, 137-139] |
| **Silica and ANCA+ Diseases** | | | | |
| WG, PSV, ANCA+ Occupational exposure (structured interview) | 5 case-control, 2 antibody present among exposed studies, and 1 case series | Positive associations seen in each of the studies: RR estimates range from 1.9 (any exposure) to 5.6; similar estimates among subtypes of disease | Higher prevalence of ANCA (anti-MPO) autoantibodies in silica exposed (i.e., patients with silicosis) (24-27%) compared with controls (0-3.7%) | [10-14] |
| **Solvents and SSc** | | | | |
| Occupational exposure (structured interview/questionnaires; job exposure matrix applied to public records); non-occupational (hobbies) exposure to solvents (structured interview) | Meta-analysis of 11 case-control studies from Europe and North America (total 1,291 cases), published 1989–2004; | From meta-analysis:<br>all studies: 2.4 (1.7–3.4)<br>adjusting for publication bias: 1.8 (1.2–2.5) | Individual RR estimates range from approximately 1.3 to 23, with most (8 of 11) between 1.3 and 3.2 | [26, 36, 38] |

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| Exposure/Disease association/Assessment method(s) | Study Designs | Results: Risk Ratio (95% CI) | Comments | References |
|---|---|---|---|---|
| | two additional cohort and two case-control studies | men: 3.0 (1.9–4.6)<br>women: 1.8 (1.5–2.1) | | |
| **Smoking and Seropositive RA** | | | | |
| Smoking history (structured interviews and questionnaires) | Meta-analysis of 16 studies from Europe and United States (total 13,885 cases), published 1987 to 2006, 1 additional cohort and 3 case-control studies from Europe, United States, and Korea (with anti-CCP+ and human leukocyte antigen shared epitope data) | From meta-analysis:<br>Men:<br>ever 1.89 (1.56–2.28)<br>current 1.87 (1.49–2.34)<br>past 1.76 (1.33–2.31)<br>20+ pack-yrs 2.31 (1.55–3.41)<br>Women:<br>ever 1.27 (1.12–1.44)<br>current 1.31 (1.12–1.54)<br>past 1.22 (1.06–1.40)<br>20+ pack-yrs 1.75 (1.52–2.02) | Higher associations with smoking seen in RF+ RA for all subjects [ever smoked RR=3.02 (2.34–3.88), current smoking RR=3.91 (2.78– 5.50), and past smoking RR=2.46 (1.74–3.47)], but in women there was not much difference between RF+ and the overall RA estimates. From subsequent studies: interaction between smoking and shared epitope genotype | [47, 52, 140-142] |
| ***Sunlight and MS (higher exposure protective)*** | | | | |
| Meteorology-based exposure (e.g., ultraviolet radiation index), occupational exposure (death certificate occupation, census data), sun exposure (structured questionnaires, actinic skin damage) | 1 cohort (occupation), 4 case-control, 1 twin, and 3 ecological studies from northern Europe, North America, and Australia (total 11,199 cases in cohort and case-control studies) | Inverse associations seen in 8 of 9 studies: RR estimates approximately 0.5 to 0.8 for occupational sun exposure, residential and other measures RR ranges from 0.25 to 0.7 | Inverse associations also seen in studies using measures of ultraviolet radiation index and other meteorological data | [71-75, 143-145] |

*Abbreviations: anti-citrullinated protein/peptide antibody (ACPA), anti-neutrophil cytoplasmic antibody (ANCA), anti-cyclic citrullinated peptide antibody (CCP), anti-myeloperoxidase antibody (MPO), primary systemic vasculitis (PSV), rheumatoid arthritis (RA), relative risk (RR), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Wegener granulomatosis (WG).

Italicized agents are protective for the development of disease.

## Table 2

Summary of the Strongest Epidemiologic Data and Research Needs Pertaining to Environmental Agents and Autoimmune Diseases *

| Environmental Agent and Autoimmune Disease | Summary of Epidemiologic Data | Research Needs |
|---|---|---|
| **Agents We Are Confident Contribute to Autoimmune Disease** | | |
| Solvents and SSc | Multiple studies in different populations with different designs and exposure assessment methods; 2-fold relative risk generally seen with “ever” exposed; publication bias considered; limited evidence of exposure-response gradient | Clarification of role of specific solvent(s), timing of exposure in relation to disease onset, effects of intensity versus duration of exposure, potential contribution of non-occupational sources of exposure; gender differences in exposure or in response to exposures; mechanism studies |
| Silica and SSc, RA, SLE, and ANCA-related vasculitis | Multiple studies in different populations with different designs and exposure assessment methods; 2-to 4-fold relative risk generally seen with “ever” exposed, evidence of exposure-response gradient | Clarification of timing of exposure in relation to disease onset, effects of intensity versus duration of exposure, potential contribution of non-occupational sources of exposure; gender differences in exposure or in response to exposures; mechanism studies |
| Cigarette smoke and seropositive RA | Multiple studies in different populations with different designs; 1.5-to 2-fold relative risk generally seen with “ever” exposed and all RA, evidence of exposure-response gradient and higher risks with anti-CCP+ RA; three studies of interaction with human leukocyte antigen genotype | Contribution of tobacco smoke (and other tobacco products) to seronegative RA and other phenotypes; gender differences in exposure or in response to exposures; mechanism studies |
| *Sunlight and MS (higher exposure is protective)* | Multiple studies in different populations with different designs and exposure measures; strong inverse associations seen; examination of age periods of effect and genetic interactions | Contribution of various sources of exposure and quantification of exposure, additional studies of exposure and age windows, mechanism studies |
| **Agents We Believe Likely Contribute to Autoimmune Disease** | | |
| Epstein-Barr virus and MS | Multiple studies showing increased antibody presence or titers in patients with MS; dose effect; one study of interaction with DR15 | Additional prospective studies establishing temporal relation between infection and disease onset |
| Early introduction of complex foods and T1D, GSE | Many studies in different populations, with different designs, but results are quite variable (positive, null, and inverse associations seen) | Clarification of role of specific antigen(s) and timing / order of introduction |
| *Dietary vitamin D and MS (higher exposure is protective)* | Supported by two prospective studies in the United States; effects seen among whites | Confirmation in other ethnic groups, examination of exposure-response, relevant periods of exposure, and potential differences in sources of dietary vitamin D |
| Solvents and MS | Multiple studies in different populations with different designs; 2-fold relative risk generally seen with “ever” exposed; publication bias not considered, exposure assessment more limited than in SSc studies | Examination in newer studies with expanded exposure assessment; clarification of role of specific solvent(s) |
| Ionizing radiation and Hashimoto thyroiditis, Graves’ disease | Multiple studies establish radiation treatment (i.e., cancer therapy) as a cause of these diseases; studies among atomic bomb survivors, populations exposed after Chernobyl, and occupationally-exposed workers show conflicting results for risk of disease and for development of anti-thyroid antibodies | Clarification of the significance of development of anti-thyroid antibodies in the absence of clinically overt disease; additional studies examining exposure-response patterns |
| Current cigarette smoke and SLE, MS | Multiple studies; more variability in results compared with RA studies, evidence of exposure-response gradient or genetic interactions not established | Clarification of potential genetic interactions or higher risk subgroups; exposure-response gradients, mechanism studies |
| Cigarette smoke and Crohn’s disease | Multiple studies showing 1.5-to 2-fold relative risk among current smokers | Clarification of potential genetic interactions or higher risk subgroups; exposure-response gradients, mechanism studies |
| Cigarette smoke and Hashimoto thyroiditis, Graves’ disease | Multiple studies; 2-to 3-fold relative risk with “ever” exposed; higher risk in patients with ophthalmologic involvement | Clarification of potential genetic interactions or higher risk subgroups; exposure-response gradients, mechanism studies |

| Environmental Agent and Autoimmune Disease | Summary of Epidemiologic Data | Research Needs |
|---|---|---|
| *Cigarette smoke and ulcerative colitis (higher exposure is protective)* | Multiple studies showing decreased risk among current smokers (RR 0.6) and increased risk (RR 1.8) among former smokers | Clarification of potential genetic interactions or higher risk subgroups; exposure-response gradients, mechanism studies |
| **Agents We Believe Are Unlikely to Contribute to an Autoimmune Disease** | | |
| Hair dyes and SLE | Multiple case control studies showing a lack of association and only a single small study suggesting an association | None |

*Abbreviations: anti-neutrophil cytoplasmic antibody (ANCA), anti-cyclic citrullinated peptide antibody (CCP), gluten-sensitive enteropathy (GSE, celiac disease), multiple sclerosis (MS), primary biliary cirrhosis (PBC), rheumatoid arthritis (RA), relative risk (RR), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and type 1 diabetes (T1D).

For italicized agents higher exposures are protective for the development of disease.