**Environmental chemicals and autoimmune disease: cause and effect.**

**Título:** Occupational exposures and autoimmune diseases.

**Resumo:** Autoimmune diseases are pathologic conditions defined by abnormal autoimmune responses and characterized by immune system reactivity in the form of autoantibodies and T cell responses to self-structures. Here we review the limited but growing epidemiologic and experimental literature pertaining to the association between autoimmune diseases and occupational exposure to silica, solvents, pesticides, and ultraviolet radiation. The strongest associations (i.e., relative risks of 3.0 and higher) have been documented in investigations of silica dust and rheumatoid arthritis, lupus, scleroderma and glomerulonephritis. Weaker associations are seen, however, for solvent exposures (in scleroderma, undifferentiated connective tissue disease, and multiple sclerosis) and for farming or pesticide exposures (in rheumatoid arthritis). Experimental studies suggest two different effects of these exposures: an enhanced proinflammatory (TH1) response (e.g., TNF-alpha and IL-1 cytokine production with T cell activation), and increased apoptosis of lymphocytes leading to exposure to or modification of endogenous proteins and subsequent autoantibody formation. The former is a general mechanism that may be relevant across a spectrum of autoimmune diseases, whereas the latter may be a mechanism more specific to particular diseases (e.g., ultraviolet radiation, Ro autoantibodies, and lupus). Occupational exposures are important risk factors for some autoimmune diseases, but improved exposure assessment methods and better coordination between experimental/animal models and epidemiologic studies are needed to define these risks more precisely.
associations with environmental and genetic factors and certain types of infections. The concordance of autoimmune diseases among identical twins is virtually always less than 50%, often in the 25-40% range. This observation, as well as epidemic clustering of some autoimmune diseases following xenobiotic exposure, reinforces the thesis that autoimmune disease is secondary to both genetic and environmental factors. In addition, because of individual genetic susceptibilities based not only on major histocompatibility complex differences but also on differences in toxin metabolism, lifestyles, and exposure rates, individuals will react differently to the same chemicals. With these comments in mind it is important to note that there have been associations of a number of xenobiotics with human autoimmune disease, including mercury, iodine, vinyl chloride, canavanine, organic solvents, silica, L-tryptophan, particulates, ultraviolet radiation, and ozone. In addition, there is discussion in the literature that raises the possibility that xenobiotics may also exacerbate an existing autoimmune disorder. In this article these issues are discussed, in particular, the evidence for the role of environmental agents in the initiation or progression of autoimmune conditions. With the worldwide deterioration of the environment, this is a particular important subject for human health. This is best illustrated by the epidemics of eosinophilic myalgia syndrome with shared characteristics that occurred about 20 years ago. Another example is the toxic oil syndrome of Spain in 1981 involving cooking oil led to both acute and chronic disease as well as formation of auto-antibodies to collagen, DNA, and skeletal muscle. Currently the question is risen whether there is a link between environmental estrogens and autoimmune disorders, especially since these illnesses are reported possibly more frequent. Yet for the time being, an answer is not available, since the current state of science with respect to autoimmunity and environmental agents is still in the early stages of hazard identification.

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[Ti] Título: Epidemiologic associations between occupational exposures and autoimmune disease: report of a meeting to explore current evidence and identify research needs.


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[Ab] Resumo: To advance understanding of autoimmunity associated with exposure to environmental factors, an [quot ]Exploratory Meeting Epidemiology on Occupational and Environmental Factors Associated with Autoimmunity[quot ] was organized in Bilthoven, the Netherlands, from May 10-12, 2000. Even if no firm conclusions can be drawn on a role of certain chemicals in the environment and in the work place in causing or exacerbating autoimmune responses and illnesses, many indications of this to occur exist. The aim of the meeting was to determine the optimal methodology for assessment of autoimmunity associated with occupational or environmental exposures in the human population, and to set up interdisciplinary and collaborative epidemiological studies to investigate the association of exposure to silica, hexachlorobenzene, ultraviolet radiation, and other agents with autoimmunity and autoimmune diseases in the human population. These agents were selected as carrying particular suspicion at present. It was concluded that there is a need for experimental studies in laboratory animals and for clinical investigations to improve scientific knowledge about the causes and mechanisms of environmentally-induced autoimmune disorders and their treatment; in addition there is a need for an interdisciplinary approach to epidemiological studies of the environmental and other causes of these disorders in human populations. Specific designs for epidemiological studies in this context, as well as laboratory assays for health outcomes, were reviewed. Several recommendations for the epidemiological approach to evaluating effects of environmental or occupational agents on autoimmunity were made. The prime recommendations are the following: 1) systematic descriptive epidemiological data on autoimmunity and autoimmune disorders are required; 2) the establishment of disease-reporting registries should be encouraged; 3) the development of internationally accepted standard diagnostic criteria for all autoimmune diseases should be encouraged; 4) the social impact of these disorders should be evaluated and estimations of direct and indirect economic costs should also be made; 5) the methods of exposure assessment used in epidemiological studies should be standardized; 6) laboratory methods for measurement of biological responses should be standardized; and 7) the inclusion of indicators of autoimmunity and autoimmune diseases and of relevant environmental exposures in ongoing epidemiological studies should be encouraged. The importance of studying environmental causes of autoimmune diseases and autoimmunity lies in the identification and prevention of risks to the public health, and in improving our knowledge of basic mechanisms of health and disease.

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[Ab] Resumo: Silica exposure has been associated with kidney disease and rheumatoid arthritis; an autoimmune mechanism has been proposed. Approximately 2 million people are occupationally exposed to silica in the United States, 100,000 at more than twice the National Institute for Occupational Safety and Health recommended exposure limit of 0.05 mg/m3(3). We examined renal disease morbidity and mortality, as well as arthritis mortality, in a cohort of 4,626 silica-exposed workers in the industrial sand industry (an industry previously unstudied). We compared the cohort with the U.S. population and also conducted internal exposure-response analyses using a job-exposure matrix based on more than 4,000 industrial hygiene samples. We found excess mortality from acute renal disease [standardized mortality ratio (SMR) = 2.61, 95% confidence intervals (95% CIs) = 1.49--4.24; 16 deaths], chronic renal disease...
(SMR = 1.61, 95% CI = 1.13–2.22; 36 deaths), and arthritis (SMR = 4.36, 95% CI = 2.76–6.54; 23 deaths) on the basis of multiple-case mortality data, which considered any mention of disease on a death certificate. Linking the cohort with the U.S. registry of end-stage renal disease for the years 1977–1996, we found an excess of end-stage renal disease incidence (standardized incidence ratio = 1.97, 95% CI = 1.25–2.96; 23 cases), which was highest for glomerulonephritis (standardized incidence ratio = 3.85, 95% CI = 1.55–7.93; 7 cases). We found increasing end-stage renal disease incidence with increasing cumulative exposure; standardized rate ratios by quartile of cumulative exposure were 1.00, 3.09, 5.22, and 7.79. A positive exposure-response trend was also observed for rheumatoid arthritis on the basis of death certificate data. These data represent the largest number of kidney disease cases analyzed to date in a cohort with well-defined silica exposure and suggest a causal link between silica and kidney disease. Excess risk of end-stage renal disease due to a lifetime of occupational exposure at currently recommended limits is estimated to be 14%, above a background end-stage renal disease risk of 2%.

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The role of metals in autoimmune vasculitis: epidemiological and pathogenic study.

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BACKGROUND: A possible relationship between Silica (Si) exposure and antineutrophil cytoplasm antibodies (ANCA)-associated vasculitis has been reported. Furthermore, tuberculosis (TBC) has been frequently described in patients with silicosis, and TBC infection shares with ANCA-associated vasculitis the formation of granulomas. Therefore, an intriguing network including Silica, Vasculitis, TBC and ANCA might be hypothesized. The aim of this work was to further investigate these correlations using both epidemiological and pathogenic approaches. METHODS: Study I—epidemiological study. A case-control study to compare the occupational histories of 31 cases of biopsy proven vasculitis (18 pauci-immune crescentic glomerulonephritis, 9 microscopic polyangitis, 4 Wegener's granulomatosis) with those of 58 age, sex and residence-matched controls (affected by other kidney diseases), was performed. Occupational Health physicians designed an appropriate questionnaire in order to evaluate a wide spread of exposures and calculate their entity by the product of Intensity x Frequency x Duration. Study II—tuberculosis association. A case-control study to evaluate the frequency of a previous history of tuberculosis (TBC) in 45 patients with vasculitis and 45 controls were performed. Study III—ANCA positivity. A case-control study to evaluate the presence of ANCA was performed by testing blood samples of 64 people with previous professional exposure and 65 sex/age matched patients hospitalized in a General Medicine Unit. Furthermore, the same evaluation was made in a pilot study in 16 patients with ongoing or previous TBC. Study IV—experimental study. The oxygen free radicals (OFR) and IL-12 production (both involved in the pathogenesis of vasculitis) from human phagocytic cells stimulated with an amorphous (diatomaceous earth) and a crystalline (quartz) form of Si at the doses of 10 and 100 microg ml(-1) was evaluated. RESULTS: Study I—a positive history of exposure to Si resulted in significantly more present in cases (14/31 = 45%) than in controls (14/58 = 24%, P = 0.04, OR = 2.4) and no other significant exposure association was found (including asbestos, mineral oil, formaldehyde, diesel and welding fumes, grain and wood dust, leather, solvents, fungicides, bitumen, lead and paint). Study II—past TBC infection was significantly more present in patients with vasculitis (12/45 = 26%) than in controls (4/45 = 8%, P < 0.05). Study III—ANCA was present in 2/64 exposed people (vs. 0/65 controls, P = NS) and 0/16 patients with TBC. Study IV—both amorphous and crystalline Si forms represented a stimulus for OFR and IL-12 production, but quartz resulted as a greater inductor. CONCLUSIONS: We conclude that Si exposure might be a risk factor for ANCA-associated vasculitis, possibly enhancing endothelial damage by phagocyte generation of oxygen free radicals and Th1 differentiation by an excessive IL-12 phagocyte production. Frequency of TBC was significantly higher in vasculitis patients. ANCA was not frequent in the preliminary examination of people with previous professional exposure or patients with TBC, but the number of samples evaluated is too small to allow conclusions.

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Autoimmune diseases associated with drugs, chemicals and environmental factors.

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Autoimmune connective tissue diseases are complex multisystems and may be life threatening. Their aetiology is unknown but genetic, hormonal and environmental factors are important. In systemic lupus erythematosus (SLE), factors such as UV light and drugs, including oestrogen, may trigger the disease; silica exposure may also be important. Scleroderma is associated with silica exposure and drugs such as bleomycin and pentazocine may induce scleroderma-like diseases. Organic solvents such as vinyl chloride and epoxy resins may also be associated with scleroderma-like illnesses. The toxic oil syndrome and eosinophilia-myalgia syndrome are best known examples of connective tissue diseases induced by chemical exposure. The systemic vasculitides and in particular cutaneous vasculitides may be induced by drugs and possibly environmental factors. A number of autoimmune connective tissue diseases may
therefore be associated with exposure to drugs, chemicals and environmental factors and the risks associated with these should be minimised where possible.

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

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The concordance of autoimmune disease among identical twins is virtually always less than 50% and often in the 25-40% range. This observation, as well as epidemic clustering of some autoimmune diseases following xenobiotic exposure, reinforces the thesis that autoimmune disease is secondary to both genetic and environmental factors. Because nonliving agents do not have genomes, disease characteristics involving nonliving xenobiotics are primarily secondary to host phenotype and function. In addition, because of individual genetic susceptibilities based not only on major histocompatibility complex differences but also on differences in toxin metabolism, lifestyles, and exposure rates, individuals will react differently to the same chemicals. With these comments in mind it is important to note that there have been associations of a number of xenobiotics with human autoimmune disease, including mercury, iodine, vinyl chloride, canavanine, organic solvents, silica, L-tryptophan, particulates, ultraviolet radiation, and ozone. In addition, there is discussion in the literature that raises the possibility that xenobiotics may also exacerbate an existing autoimmune disease. In this article we discuss these issues and, in particular, the evidence for the role of environmental agents in the initiation or progression of autoimmune conditions. With the worldwide deterioration of the environment, this is a particularly important subject for human health.