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# Environmental xenobiotic exposure and autoimmunity

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**Abstract**

Susceptibility to autoimmune diseases is dependent on multigenic inheritance, environmental factors, and stochastic events. Although there has been substantial progress in identifying predisposing genetic variants, a significant challenge facing autoimmune disease research is the identification of the specific events that trigger loss of tolerance, autoreactivity and ultimately autoimmune disease. Accordingly, studies have indicated that a wide range of extrinsic factors including drugs, chemicals, microbes, and other environmental factors can induce autoimmunity, particularly systemic autoimmune diseases such as lupus. This review describes a class of environmental factors, namely xenobiotics, epidemiologically linked to human autoimmunity. Mechanisms of xenobiotic autoimmune disease induction are discussed in terms of human and animal model studies with a focus on the role of inflammation and the innate immune response. We argue that localized tissue damage and chronic inflammation elicited by xenobiotic exposure leads to the release of self-antigens and damage-associated molecular patterns as well as the appearance of ectopic lymphoid structures and secondary lymphoid hypertrophy, which provide a milieu for the production of autoreactive B and T cells that contribute to the development and persistence of autoimmunity in predisposed individuals.

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**Keywords**

Xenobiotic, Autoimmunity, Animal model, Inflammation, Epidemiology.

## 1. Introduction

In this review, we examine the development of autoimmunity elicited by exposure to environmental factors with emphasis on chemical agents often referred to as xenobiotics because they contain foreign chemical substances not naturally produced by or present in organisms. Xenobiotics are present in the air we breathe, the fluids we drink, the food we eat, synthetic and natural chemicals, and industrial by-products. Linking exposure to these agents with human autoimmune disease manifestations is difficult because of the inherent limitations of epidemiological studies to draw causal conclusions [1]. Furthermore, human populations are rarely exposed to a single agent over time, there can be a significant delay between exposure and disease onset, and it is often not possible to identify all of the toxicants to which a population has been exposed [2]. Additionally, the magnitude of autoreactivity following human xenobiotic exposure can differ with some xenobiotics inducing clinical disease [1] while others trigger features of autoimmunity without evidence of overt disease [3]. Differences in autoreactivity can also reflect the degree of exposure [4] or the extent of genetic predisposition. Consequently, it is not surprising that only a few xenobiotic agents have been established to promote autoimmune disease in humans. However, many of these limitations can often be overcome by studying experimental animal models, which have confirmed the autoimmune-promoting potential of certain xenobiotics and have also provided insights into pathogenic mechanisms. Therefore, this review draws from both human and animal research in describing the role of xenobiotic exposure in autoimmunity.

## 2. Autoimmunity

Autoimmunity is the reaction of cells or products of the immune system with constituents of the body's own tissues leading to pathology and disease. Autoimmunity is responsible for a variety of clinical conditions with common features including expansion of self-reactive T and B cells, production of autoantibodies, and tissue damage. The most challenging aspect of autoimmunity is identifying the events that promote the initiation of the response. While many intrinsic factors including age, sex, and genetics contribute to autoimmunity, it is believed that extrinsic factors such as drugs, chemicals, and microbes may be triggers that initiate autoimmune responses [5].

## 3. Autoimmune diseases associated with environmental exposure

Autoreactivity has been argued to lead to three distinct yet overlapping clinical consequences reflecting the severity of self-reactivity [5]. A physiological level of self-reactivity is required for lymphocyte selection and immune homeostasis and is not associated with autoimmunity. Early or mild loss of tolerance is thought to produce a pre-clinical form of autoimmunity limited to detectable autoantibodies and minor cellular infiltrates. Finally, autoreactivity can progress to pathogenic autoimmunity in which there is clinically significant cell or tissue damage. Notably, xenobiotic exposures can affect all three of these autoreactive states. Several xenobiotics were shown to impact immune system development [6], some exposures such as mercury can lead to predominantly preclinical features [3], while crystalline silica exposure can result in several clinical syndromes [1].

Xenobiotic exposure can promote autoimmunity by the de novo triggering of autoimmunity in healthy individuals, by exacerbating underlying idiopathic autoimmunity, or by inducing xenobiotic-specific autoimmunity against a backdrop of idiopathic disease [7–9]. Differentiating between these possibilities is challenging because of the lack of accepted criteria for the diagnosis or classification of environmentally associated autoimmunity [2]. Moreover, it is unclear to what extent idiopathic and induced diseases arise by common mechanisms [7,10]. For example, the same agent can induce different autoimmune disorders, e.g., silica [1], while multiple agents can produce a similar clinical picture, i.e., different drugs leading to similar lupus-like syndromes [8]. Other environmental exposures, including toxic oil syndrome and eosinophilia myalgia syndrome, exhibit unique clinical features that allowed the development of syndrome-specific classification criteria and which suggests exposure-specific disease mechanisms [11–13].

A recent analysis [1] examined the epidemiological evidence for relationships between xenobiotic exposures and human autoimmune diseases, identifying "confident", "likely" and "unlikely" associations (Table 1). Exposure-disease associations supported by multiple studies resulted in high confidence that certain exposures contribute to disease development. For example, occupational exposure to crystalline silica has been linked to several autoimmune diseases including rheumatoid arthritis (RA), systemic sclerosis (SSc), SLE and anti-neutrophil cytoplasmic antibody (ANCA)-related diseases. Solvents, or chemicals with similar structures, including vinyl chloride, epoxy resin, trichloroethylene (TCE), perchloroethylene, or mixed solvents were confidently associated with SSc. Other studies supported a likely association between solvent exposure and multiple sclerosis (MS). Many studies have identified smoking as a strong risk activity for RA particularly if autoantibody positive, while fewer studies identify smoking as a risk for other autoimmune diseases such as SLE, MS, and thyroid autoimmunity. A complicated association has been reported for smoking and inflammatory bowel disease, with smoking argued to contribute to Crohn's disease, but to protect from ulcerative colitis. There is some evidence for an association of cosmetics with SLE, RA and primary biliary cholangitis (PBC) [1,14]. Finally, the association of hair dye exposure with SLE was considered unlikely [1].

Although criteria for the diagnosis of environmental-associated autoimmune disease remain to be established [2], there are several circumstances that might

**Table 1** Environmental exposures and human autoimmune diseases.

| Environmental agent[a] | Autoimmune disease | Sex bias | Exposure |
|---|---|---|---|
| Confident | | | |
| Crystalline silica | RA#, SSc, SLE, ANCA | SLE, none<br>SSc, male<br>RA, none | Occupational |
| Solvents | SSc | Male | Occupational |
| Smoking | Seropositive RA | Increased risk higher in males | Lifestyle |
| Likely | | | |
| Solvents | MS | Increased risk for male and female dependent on sex biased occupation | Occupational |
| Smoking | SLE, MS, Crohn's disease, Hashimoto thyroiditis, Grave's disease<br>Ulcerative colitis[b] | (insufficient data) | Lifestyle |
| Unlikely | | | |
| Hair dyes | SLE | – | Lifestyle |

# Abbreviations: RA, rheumatoid arthritis; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; ANCA, anti-neutrophil cytoplasmic antibody; MS, multiple sclerosis.

[a] Does not include biological (virus, bacteria), dietary (food, supplements).

[b] Protective.