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Can xenobiotics contribute to the increase in the incidence of endocrine diseases by inducing autoimmune processes?

Bogusława Budziszewska[1], Beata Starek-Świechowicz[1], Stanisław Zieliński[2], Lucyna Pomierny-Chamioło[1]

[1] Department of Toxicological Biochemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland
[2] Department of Clinical Pharmacy, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland

Corresponding author: Lucyna Pomierny-Chamioło, Ph.D., Assoc.Prof.
Department of Toxicological Biochemistry, Faculty of Pharmacy, Jagiellonian University Medical College
ul. Medyczna 9, 30-688 Kraków, Poland
E-mail: lucyna.pomierny-chamiolo@uj.edu.pl

Abstract: In recent decades, there has been an increase in the incidence of both autoimmune and endocrine diseases, mainly in industrialized countries and may be partly due to human exposure to increasing levels of environmental pollutants. Research shows that environmental pollutants, specifically endocrine disrupting compounds (EDCs), adversely affect gonadal and thyroid function and are linked to type 1 diabetes development. Current data illustrates that the immune system is also a target of EDCs, including the possible exacerbation of autoimmune processes, which are the causes of many endocrine diseases.
In this paper, we have presented evidence that environmental pollutants, in addition to directly affecting endocrine glands, can also damage them by intensifying autoimmune processes. We collected experimental and epidemiological data on the effects of EDCs on testicular, ovarian and thyroid function, as well as on the impact of these compounds on the development of type 1 diabetes. The available data demonstrating the potential for particular EDCs to exacerbate autoimmune processes in selected autoimmune endocrine diseases, such as autoimmune orchitis, premature ovarian failure, autoimmune thyroid diseases, and type 1 diabetes were also shown. Because research demonstrating the effects of EDCs on the immune system and the involvement of these compounds in the pathogenesis of autoimmune endocrine diseases is in its early stages, we also presented scientific doubts about this problem and directions for further research. Confirmation of this mechanism of action of EDCs in further studies would help to clarify the current controversies regarding the assessment of their effects in humans.

Keywords: environmental pollutants, endocrine disrupting compounds, autoimmune endocrine diseases, loss of self-tolerance, molecular mechanisms.

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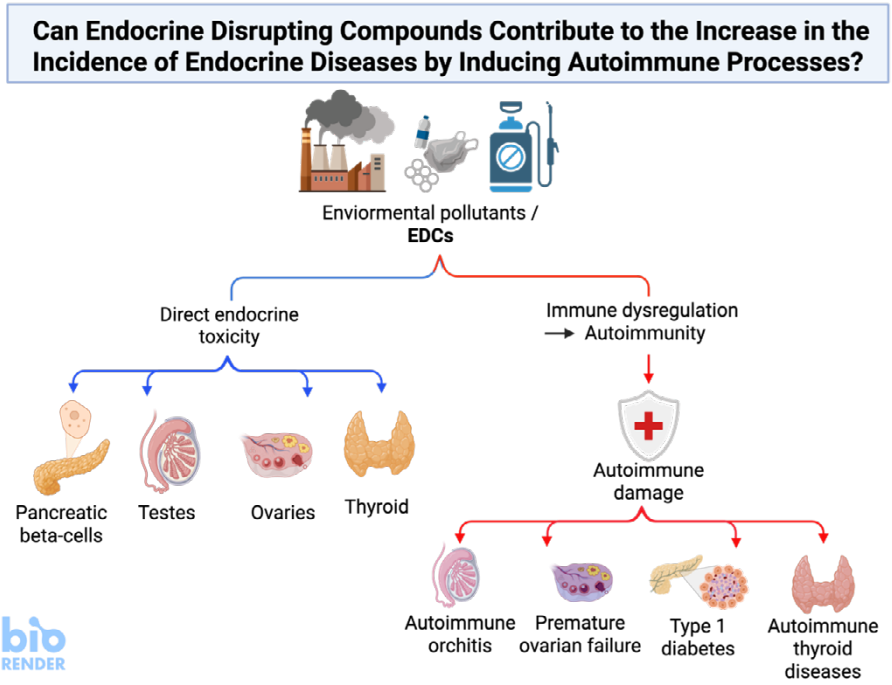
Graphical abstract



Introduction

In recent decades, an increase in the occurrence of autoimmune diseases has been observed, especially in industrialized countries [1]. Genetic predispositions, mainly genes related to the functioning of the immune system, including human lymphocyte antigen (HLA) alleles, increase the risk of developing autoimmune diseases, but many environmental factors such as infections, diet and xenobiotics also play an important role in the emergence of these diseases [2]. Some studies indicate that exposure to environmental pollution, including endocrine disrupting compounds (EDCs), may disturb the function of the immune system and consequently contribute to the induction or exacerbation of autoimmune processes in individuals with genetic susceptibility [3]. Thus, the worldwide increase in environmental pollutants may be a significant factor responsible for the increased incidence of autoimmune diseases. Similar to autoimmune diseases, endocrine disorders, especially those in which autoimmune processes cause damage to an endocrine gland, e.g. the thyroid, ovaries, testicles, adrenal glands or pancreatic beta cells, are also increasingly diagnosed and, in their pathogenesis, the significant role of environmental pollution is also suggested [4]. Because the immune and endocrine systems are interconnected, there is now emerging evidence that environmental toxins, in addition to their direct effect on the endocrine glands, can also disrupt hormonal function by intensifying autoimmune processes, even when at lower doses. The present paper presents the results of epidemiological studies, as well as some conducted in experimental animals and *in vitro* on the participation and potential mechanisms of

action of selected environmental chemicals in the induction of autoimmune processes and their possible impact on endocrine system disorders. In particular, xenobiotics associated with the risk of developing diseases such as type 1 diabetes, autoimmune thyroid disorders and autoimmune inflammation of the ovaries and testicles, and their potential impact on the immune system and the disturbance of the tolerance process, are presented.

Autoimmune diseases

Autoimmune diseases affect about 5–8% of the population and comprise diverse chronic conditions caused by an abnormal immune response against self-antigens [5]. They arise from interacting genetic and environmental factors. Genetic susceptibility contributes ~20–30% and environmental factors ~70–80% of risk [2, 6].

Autoimmune diseases may involve the whole body or specific organs. They are classified as organ-specific (e.g., Hashimoto's disease, Graves's disease, Addison's disease, pemphigus vulgaris, multiple sclerosis) or systemic (e.g., systemic sclerosis, systemic lupus erythematosus). Another division reflects the dominant immune arm: cellular (e.g., Hashimoto's disease, type 1 diabetes, multiple sclerosis) versus humoral (e.g., pemphigus vulgaris, myasthenia gravis, Graves' disease, systemic lupus erythematosus). Autoimmunity stems from failed self-tolerance, leading to immune activation against self. Central tolerance in bone marrow and thymus relies on negative selection, while peripheral tolerance involves deletion, anergy, and active suppression.

Loss of tolerance may result from reduced Treg/Breg function, imbalance of pro- and anti-inflammatory cytokines, mutations enabling autoreactive T-cell survival, and rapid dendritic-cell maturation under pro-inflammatory stimuli. Antigen binding to the T-cell receptor triggers activation, proliferation, and differentiation, while counter-regulatory processes promote CD4+-Foxp3+ regulatory T cells that enforce self-tolerance [7]. Genetic predisposition, especially certain HLA alleles, increases risk but is not sufficient alone.

Autoimmune diseases are heterogeneous. Etiologic factors and mechanisms remain incompletely defined, and new ones continue to be identified. Candidate environmental risks include bacterial or viral infections, exposure to xenobiotics, reactive oxygen species, ultraviolet radiation, diet, gut microbiome dysfunction, and lifestyle factors [8].

Exposure to environmental pollutants

Human exposure to pollutants from natural (fires, volcanoes, rock erosion) and anthropogenic sources (industry, power plants, mining, waste incineration, transport), as well as to food additives, household products, cosmetics and medicines, is increasing due to the continual introduction of new compounds and technologies [2].

Persistent organic pollutants (e.g., polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins (PCDDs), organochlorine pesticides) resist degradation and accumulate in the environment and food chain, whereas non-persistent pollutants (e.g., phthalates, bisphenols such as bisphenol A (BPA)) have short environmental half-lives and low human bioaccumulation.

Compounds shown to adversely affect endocrine function include heavy metals, PCBs, PCDDs, polyfluoroalkyl substances (PFAS), phenols, phthalates, pesticides and solvents [9, 10].

A special subgroup are EDCs, a heterogeneous set of compounds with affinity for sex-hormone receptors, mainly estrogen receptors (ERs).

The EDCs group includes, among others:

- *Bisphenols*: (e.g., BPA): Used in plastics; present in food containers, packaging, and cans.
- *Phthalates*: Salts and esters of phthalic acid used as plasticizers; found in some varnishes, paints, adhesives, laminates, films, and cosmetics.
- *PCBs*: Persistent pollutants; main human exposure is via animal-derived foods (meat, fish, dairy).
- *PCDDs*: (e.g., 2,3,7,8-Tetrachlorodibenzodioxin (TCDD)): Formed mainly during industrial and municipal waste incineration; TCDD is the most toxic congener.
- *Parabens*: (methyl-, ethyl-, propyl-, butylparaben): Preservatives in cosmetics and food packaging.
- *Triclosan*: A chlorinated phenol with antimicrobial properties; used in disinfectants, cosmetics, household chemicals, and textiles.
- *Benzophenones*: (BP-1, BP-2, BP-3): UV filters used in cosmetics, textiles, and food packaging.
- *Polycyclic aromatic hydrocarbons* (PAHs): Persistent pollutants with fused aromatic rings; generated during waste incineration and thermal food processing.
- *Per- and polyfluoroalkyl substances* (PFAS): Highly resistant to degradation; found in nonstick cookware and food packaging; accumulate in the human body.
- *Pesticides*: Organochlorines: Persistent in the environment (dichlorodiphenyltrichloroethane (DDT), methoxychlor, dieldrin, chlordane) and organophosphates: Acetylcholinesterase inhibitors (malathion, parathion, chlorpyrifos).

These compounds contaminate water, food, and air. For example, they can leak from food packaging into food. If present in the air, they can be absorbed through the respiratory tract. If in contact with skin, they can be absorbed through the skin. The presence of many of these compounds or their metabolites has been demonstrated in humans in blood or urine, as well as in the placenta of pregnant women and in breast milk. For example, BPA has been detected in approximately 90% of the population in industrialized countries [11].

Currently, there is a trend toward a higher incidence of endocrine diseases in children and adults, which cannot be fully explained by lifestyle changes, including dietary changes [12]. Therefore, exposure to EDCs is perceived as a significant factor that may disrupt endocrine system functions.

The influence of environmental pollutants on testicular function

Many experimental studies show that environmental pollutants, especially EDCs, are toxic to the gonads and may contribute to the recent decline in human fertility. Beyond testes and ovaries, these compounds adversely affect the thyroid, central nervous system, cardiovascular system, and immune system.

The key determinant of male fertility is semen quality, which has declined for decades (≈1–3% per year; 50% from 1938–1990; 32% from 1989–2005) in Europe and Asia [13]. Causes remain unclear, but exposure to pollutants (notably EDCs) and oxidative stress are major suspects in testicular dysfunction. In animals, pesticides, herbicides, BPA, di(2-ethylhexyl)phthalate (DEHP), PCBs, heavy metals, acrylamide, 3-methyl-4-nitrophenol, microplastics, and benzophenone-2 disrupt testicular function [14–17]. Although some studies find no association, current evidence suggests stronger effects with prenatal exposure than adult exposure, indicating heightened developmental vulnerability and long-term reproductive consequences. For example, prenatal

exposure to phthalate mixtures or DEHP impairs Leydig and Sertoli cell maturation, reducing germ cell number and adult testosterone production [18, 19].

Epidemiologic data are fewer than experimental data, but most also indicate adverse effects of environmental toxicants on testicular function [12, 20]. Findings center on BPA, PFAS, and DEHP, with higher urinary BPA levels correlating with lower sperm count, viability, and motility, and with increased sperm DNA damage [21]. PFAS levels are inversely associated with sperm motility and number and are linked to abnormal morphology [22–24]. In humans, as in animals, prenatal EDC exposure, particularly PFAS, is associated with reduced sperm count and concentration and elevated LH/FSH in male offspring in young adulthood [25, 26]. The prenatal window appears critical. Estrogenic or antiandrogenic insults during gonadal development can cause subtle testicular dysgenesis that emerges at puberty as reduced testosterone and impaired spermatogenesis, while low prenatal testosterone is linked to poor penile development, decreased semen quality, mild hypospadias, and higher testicular cancer risk [27].

Mechanism of action of environmental pollutants on testicular function

Most data indicate that EDCs, including BPA, phthalate diesters, and PFAS, impair testicular function mainly via estrogenic, antiandrogenic, and pro-oxidative actions. *In vitro* and *in vivo* studies show EDCs can bind estrogen and/or androgen receptors, acting as agonists or antagonists, thereby disrupting sex hormone-regulated processes, especially sexual development and gonadal function. For testicular function, estrogenic agents (e.g., BPA) and antiandrogens (e.g., phthalates) are particularly concerning because estrogens in males suppress the hypothalamic-pituitary-gonadal axis [12]. Still, some question a primary receptor-mediated mechanism, as EDC affinity for ERα/ERβ is ~1,000–10,000× lower than that of 17β-estradiol *in vitro* [28].

Adverse effects may also arise from oxidative stress, disruption of the blood-testis barrier, reduced thyroid hormones, aryl hydrocarbon receptor (AhR) agonism, and immune activation. Oxidative stress from exposures such as heavy metals and persistent organic pollutants is linked to increased apoptosis, sperm DNA damage, impaired motility, and reduced fertilization potential [29].

Current research also points to immune effects. Epidemiologic studies report associations between environmental toxins and autoimmune disease, for example, urinary BPA and bisphenol F with systemic lupus erythematosus [30], PCB exposure with autoimmune rheumatic diseases [31], and, after chlordane exposure, higher frequencies of antinuclear, anti-DNA, and anti-smooth muscle antibodies [32].

Although no studies directly link a specific pollutant to autoimmune-mediated endocrine-gland injury, many pollutants modulate immunity and pathways that underlie loss of self-tolerance and autoimmunity. Infection and inflammation of the reproductive tract are major causes of male infertility, yet non-infectious inflammation of the testis and epididymis remains poorly understood. Autoimmune orchitis features lymphocyte/macrophage infiltration and anti-sperm antibodies (ASA), leading to sperm abnormalities and infertility [33]. The testis is immunoprivileged and haploid germ cells expressing novel autoantigens arise after immune tolerance is set. Under physiologic conditions, the blood-testis barrier (mainly Sertoli cells), the *Aire* gene, and ABC transporters shield germ cells from autoimmune attack [34]. Histopathology in infertile men shows frequent inflammation, but because human biopsies are scarce, most data come from animal models-notably experimental autoimmune orchitis (EAO) induced by immunizing susceptible A/J mice with syngeneic testicular germ cells [34].

DEHP is relatively well studied, while not itself immunogenic, it heightens testicular susceptibility to autoimmune damage [34, 35]. It also alters Sertoli cells, potentially disrupting the blood-testis barrier [36]. Low-dose DEHP, which does not directly impair spermatogenesis, remodels the testicular immune microenvironment in mice, causing lymphocyte infiltration, increased interferon-γ, and a modest rise in anti-germ-cell autoantibodies [34]. Cadmium shows similar potentiation of autoimmunity, necrotic at high doses, but at low doses only mildly disturbs spermatogenesis while increasing autoimmune susceptibility [37]. Our rat studies likewise show that benzophenone-2 (BP-2), a UV-filter EDC, worsens semen parameters (lower count and motility with more morphological defects), alters sex hormones (lower testosterone and higher 17β-estradiol), and reshapes the testicular immune milieu [38]. Specifically, BP-2 decreases resident anti-inflammatory macrophages (CD68-CD163+; M2) and increases pro-inflammatory macrophages (CD68+CD163–; M1 "newly arrived"), shifts the CD4+:CD8+ T-cell ratio toward CD8+, and increases testicular B cells [38]. These T-cell and macrophage shift parallel those observed in EAO [39].

Overall, limited evidence suggests that for some pollutants that affect both immunity and testicular function, induction of autoimmunity may be a key mechanism of gonadotoxicity.

The influence of environmental pollutants on female fertility

Although fewer than studies on testicular toxicity, several reports show adverse effects of organochlorine pesticides, heavy metals, BPA, PCDDs, PCBs, nonylphenol, triclosan, and parabens on ovarian function in women and in adult animal models [40, 41]. In animals, typical findings include increased preantral follicle atresia, disrupted follicle maturation, steroidogenesis, and folliculogenesis as well as uterine, hypothalamic, and pituitary changes, and reduced fertility [40]. Human data are limited but likewise suggest reduced fertility, for example, exposure to organochlorine pesticides, PCBs, parabens, or dioxins is associated with longer time to pregnancy [42]. Some PCB or dioxin exposures are also linked to endometriosis, anovulation, and uterine fibroids [41, 43].

In animals, EDC effects often reverse after exposure ends, but fetal exposure can produce lasting reproductive deficits. In humans, prenatal EDC exposure has been associated with hypospadias, cryptorchidism, reduced fertility, and testicular cancer in men, and with ovarian dysfunction, infertility, and breast cancer in women [44].

Mechanism of action of environmental pollutants on female fertility

EDCs likely impair ovarian function via ER and AhR signaling, oxidative stress, and altered steroid metabolism, but the immune system may also be a direct target. Environmental EDCs that modulate immunity may promote ovarian autoimmunity [45]. Autoimmune involvement in premature ovarian failure (POF) is supported by lymphocytic oophoritis, ovarian autoantibodies, and frequent co-occurrence with other autoimmune diseases, most notably Addison's disease, but also autoimmune thyroiditis, type 1 diabetes, celiac disease, rheumatoid arthritis, and systemic lupus erythematosus [46]. Idiopathic infertility may likewise reflect autoimmunity: infertile women more often harbor antibodies against ovarian components (e.g., ooplasm, zona pellucida, granulosa cells) and also antinuclear, antiphospholipid, thyroid peroxidase autoantibody (TPOAb), and thyroglobulin autoantibody (TgAb) [47]. No causal link between EDC exposure and POF is established, but these compounds affect pathways central to its pathogenesis. Vabre *et al.* summarized reductions in the primordial follicle pool (PAH, DEHP), follicular atresia via oxidative stress/

apoptosis (BPA, DEHP, dibutyl phthalate, PAH, pesticides, dioxin), and premature activation/exhaustion of resting follicles (DEHP, BPA), implicating these agents in POF mechanisms [45]. Autoimmunity is also suggested in polycystic ovary syndrome (PCOS), with elevated antihistone and anti-dsDNA antibodies in affected women [48]. Autoimmune mechanisms may contribute to recurrent pregnancy loss, and several clinical studies link pesticides and plasticizers to this disorder via hormonal and immune disruption [49]. EDC exposure before or during conception may impair maternal immune tolerance to paternal antigens and hinder implantation [49, 50]. Clinically, higher PFAS levels in follicular fluid correlate with lower IVF pregnancy rates [51].

EDCs may drive ovarian autoimmunity through ER and AhR expressed on immune cells and by increasing proinflammatory cytokine secretion, thereby amplifying autoimmune processes [52, 53].

The influence of environmental pollutants on thyroid function

Beyond gonadotoxicity, adverse effects of EDCs on thyroid function are relatively well studied. EDCs can disrupt thyroid hormone action not only via weak agonism/antagonism or receptor modulation, but also by altering hormone synthesis, transport, metabolism, and receptor abundance [54]. Most data show reduced free or total T4/T3 and inverse associations between urinary levels of phthalates, BPA, and organochlorines and serum T4. Still, findings for T3, T4, and TSH are inconsistent, and some compounds impair thyroid hormone function without changing circulating levels [54–57]. Similar to gonadal effects, thyroid impacts are most evident after prenatal exposure.

Autoimmunity frequently underlies thyroid dysfunction. Hashimoto's disease (primarily hypothyroidism) and Graves' disease (hyperthyroidism) are increasingly common and more prevalent in women. In Hashimoto's thyroiditis, autoantibodies against thyroglobulin and thyroperoxidase drive inflammation and gland damage, while in Graves' disease, TRAb elevates thyroid hormone levels.

Some data indicate that environmental and occupational EDC exposure may raise antithyroid antibodies [10]. For example, residence in areas with high organochlorine pesticides is linked to features of autoimmune thyroiditis, higher serum TPOAb and TSH and hypoechogenicity [58]. Prior work also found that occupational/environmental exposure to PCBs, PCDDs, and dibenzofurans was associated with higher TPOAb, TgAb, and TRAb [59]. Similarly, women exposed to PCBs and hexachlorobenzene showed elevated TPOAb [60].

Studies of prenatal BPA exposure report an inverse relationship between maternal BPA and offspring TSH, while thyroid hormone levels show no change or bidirectional changes [61]. Among EDCs, most evidence implicating them in autoimmune thyroid disease concerns BPA, but results are mixed: Sur *et al.* found no difference in urinary BPA between Hashimoto's patients and controls [62], whereas another study linked serum BPA with TPOAb and TgAb, but not thyroid-stimulating hormone receptor autoantibody (TRAb) [63].

BPA's immune effects likely involve ER, AhR, and peroxisome proliferator-activated receptors (PPARs). Its estrogen-like actions, such as increased T-cell proliferation, skewing toward Th1, higher antibody production, and reduced regulatory T cells, may promote autoimmunity [64].

The influence of environmental pollutants on diabetes type 1 development

Type 1 diabetes is a T cell-mediated autoimmune disease increasingly common in industrialized countries and it destroys pancreatic β cells and causes insulin deficiency. About 90% of patients have autoantibodies to insulin, glutamic acid decarboxylase (GAD), islet antigen-2, or zinc

transporter-8 that appear months to years before symptoms. Genetic influence appears smaller than that of early environmental factors [65].

Proposed triggers of islet autoimmunity and progression to overt disease in genetically susceptible people include viral infections, higher birth weight, childhood diet and weight gain, microbiome disturbances, vitamin D deficiency, and environmental toxins.

Epidemiologic data on pollutants and type 1 diabetes remain sparse and inconclusive [9, 66]. Occupational PCB exposure has been linked to a fourfold increase in serum anti-GAD autoantibodies [67], though autoantibodies can precede disease by years and are not uniformly predictive. Higher organochlorine/organophosphorus pesticide levels have been reported in children with type 1 diabetes [68], and serum PCBs were ~30% higher in pregnant women with diabetes than controls [69]. Other studies, however, show no association between specific pollutants and β-cell autoimmunity or clinical type 1 diabetes. Salo *et al.* found no link between prenatal/early-life pollutant levels and later disease [70].

Additional evidence comes from animal and *in vitro* models [9]. In type 1 diabetes models, BPA accelerates disease development [71], whereas TCDD or certain PCB congeners reduce it [72]. Some EDCs (e.g., triphenyltin, polybrominated diphenyl ethers) inhibit insulin secretion and worsen hyperglycemia while others correlate with type 2 diabetes (e.g., DDT, PFAS, phthalates, PAHs) or enhance autoimmune mechanisms (e.g., phthalates, PAHs), but links to type 1 diabetes remain limited and inconsistent [66]. Beyond EDCs, several studies associate nitrate exposure with type 1 diabetes [73].

Mechanistically, EDCs may induce oxidative stress and mitochondrial dysfunction, increasing β-cell apoptosis, impairing β-cell replication, activating AhR, damaging DNA, and provoking inflammation. Pollutants may also act via immune cells. Many exert AhR agonism, potentially impairing Treg function and amplifying autoimmunity [74]. AhR effects are ligand- and time-dependent. TCDD is toxic to rat β cells *in vitro* via AhR, yet in NOD mice it prevents diabetes when given at insulitis onset [66, 75]. Similar TCDD-driven immunosuppression, likely via AhR and Treg induction, appears in allergy and lupus models, underscoring ligand-specific outcomes [76].

Environmental pollution may further promote type 1 diabetes by shifting cytokine balance, inducing early-life epigenetic changes, or increasing intestinal permeability.

The mechanism of EDCs action on the autoimmunity process

The primary mechanism by which EDCs act is interference with steroid-hormone receptors, mainly ER, and disruption of hormone-dependent processes (Fig. 1). Through ERs, these compounds can affect dendritic cells, B cells, T cells, and innate immune cells [4]. Because autoimmune diseases, especially endocrinopathies, are far more common in women, estrogen's role in promoting autoimmunity is heavily studied [5, 77]. Estrogens signal via nuclear ERα/β on most immune cells and can also modulate transcription through AhR, PPAR, NFκB, and AP-1 [78]. They additionally act via membrane receptors (e.g., GPR30) on immune cells, mediating rapid nongenomic effects. Many studies implicate estrogens in activating autoreactive T and B cells and increasing autoantibody production, but their exact contribution to sex-biased autoimmunity remains unresolved [78]. Other factors, such as X-linked genes, microRNAs, and sex-specific epigenetics, also likely contribute. Estrogen effects vary with concentration, mechanism, and receptor expression across immune cells, explaining model-to-model differences [77]. In systemic lupus erythematosus, higher 17β-estradiol and lower androgens accelerate disease and worsen

symptoms [79]. In women, SLE rises after puberty, falls after menopause, and varies across the cycle and pregnancy; in both sexes with SLE, estrogen levels are higher and androgens lower than in the general population. Sex-based immune differences likely hasten loss of tolerance, autoantibody production, and autoimmunity in genetically predisposed women [80]. Impaired Treg stability/survival in autoimmunity partly reflects cytokine shifts; estrogens increase IL-6 in many cells, contributing to Treg deregulation [5].

Beyond IL-6, Treg function depends on local cytokines from dendritic cells, macrophages, and T-cell subsets. Because 17β-estradiol alters key Treg-relevant cytokines (IL-4, IL-10, IL-12, IL-17, TNF-β) in a dose-dependent manner, it may shape sex-biased responses and amplify EDC-driven autoimmunity [81]. EDCs acting through ERs can skew the balance of pro- and anti-inflammatory cytokines; human studies link exposure to bisphenols, parabens, and benzophenones with inflammatory markers [52, 82–84]. In humans, exposure to chlordane or TCDD has also been associated with fewer suppressor T cells and more antinuclear antibodies [79].

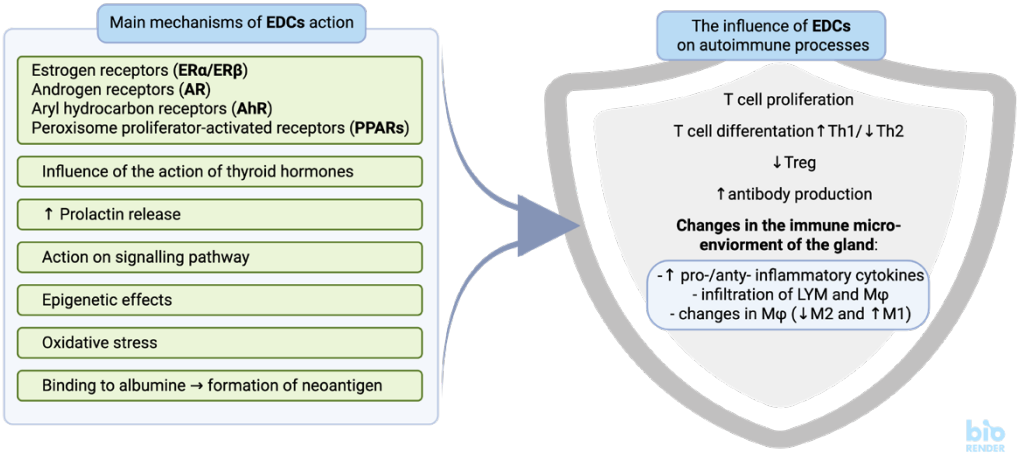


Fig. 1. Main mechanisms of EDCs action and their autoimmune results. LYM — lymphocytes, MΦ — macrophages.

Because *in vitro* data show EDC affinity for sex-hormone receptors (including ER) is much lower than for native hormones, EDC-driven autoimmunity likely involves additional mechanisms.

A key pathway is AhR activation. AhR helps balance Treg cells versus Th17 (IL-17–producing) and Th22 (IL-22–producing) cells, which are central to autoimmunity [85]. TCDD, an AhR ligand, augments receptor responses to endogenous activators and modulates dendritic cells, Tregs, Th17, and Th22 [85]. (Fig. 2 outlines the putative mechanism.) Vietnam War veterans exposed to TCDD-contaminated defoliants had a 2.5- to 3-fold higher incidence of Graves' disease while TCDD-induced Treg/Th17/Th22 disturbances resembled those in Graves' and Hashimoto's thyroiditis [85]. PFAS, BPA, phthalates, PCBs, and PAHs can also shift cytokine balance in human and murine cells *in vitro*, a change linked to autoimmunity [66]. AhR effects are ligand-, dose-, exposure-, and pathway-dependent [86]. In some models, EDCs suppress autoimmunity: TCDD promotes Treg formation, reduces Th17, and prevents experimental autoimmune encephalitis, whereas the short-acting ligand 6-formylindolo[3,2-b]carbazole drives the opposite

Treg/Th17 shift and worsens disease [87]. Likewise, despite possibly worsening thyroid autoimmunity, TCDD prevents type 1 diabetes in a mouse model [75, 85].

Beyond ERs and AhR, EDCs may also act via PPARs. PPARγ regulates T-cell activation, proliferation, and differentiation, and phthalates and perfluorinated compounds may influence autoimmune mechanisms by activating this receptor [88, 89].

EDCs can induce early-life epigenetic changes (histone modifications, DNA methylation, microRNA dysregulation), potentially by disrupting immune tolerance and elevating autoimmune risk [90]. For ovaries, fetal/neonatal methoxychlor exposure alters methylation and impairs adult function in rats [91]. Gamete-epigenome changes can be transgenerational: prenatal BPA or BPS alters transcription in neonatal spermatogonia, reduces adult sperm counts, and some effects persist to F3 [92].

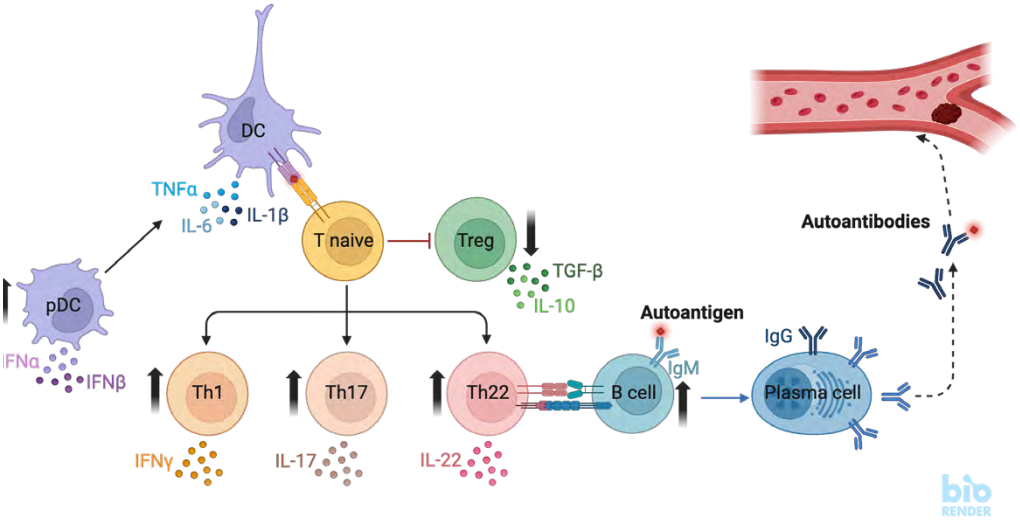


Fig. 2. Potential effects of some environmental pollutants on autoimmune processes. pDC — plasmacytoid dendritic cells; DC — dendritic cells; Th — T helper cells; T naive — T naive cells. The arrows indicate the effect of EDCs on the immune cell subpopulation. Data based on [5, 34, 35, 58, 60, 66, 79, 81, 85, 88, 89].

Other mechanisms may also contribute to EDC-driven autoimmunity, including exacerbated oxidative stress (via glutathione depletion), direct signaling-pathway effects, interactions with thyroid-hormone receptors, increased prolactin release, reduced expression of proteins that regulate autoimmunity, protein modification, and neoantigen formation [93, 94].

The influence of bisphenol A on the process of neoantigen formation

Mechanisms by which EDCs disrupt immune tolerance are being investigated in autoimmune animal models and *in vitro*. The most studied is bisphenol A (BPA), produced in large quantities and widely used, leading to high human exposure.

BPA binds ERs, acting as an agonist or antagonist at ERα and as an agonist at Erβ, and also interacts with AhR and PPAR [95]. Via estrogenic pathways, BPA alters T-cell subsets, B-cell

function, and dendritic-cell activity [64]. Most studies indicate that through ER, AhR, and PPAR signaling, BPA shifts Th1/Th2 polarization toward Th1, changes cytokine profiles, lowers Treg levels, and increases B-cell antibody production [64]. BPA may also intensify autoimmunity by generating neoantigens.

Free BPA can bind serum proteins, primarily albumin, inducing allosteric changes that create neoantigens and trigger immune responses. In Parkinson's disease, impaired BPA biotransformation permits greater binding to human serum albumin (HSA) and neuronal protein disulfide isomerase (PDI). Individuals with high BPA-HSA or anti-PDI antibodies (which damage PDI, promote protein misfolding, and α-synuclein aggregation) show higher risk of elevated anti-α-synuclein antibodies, a hallmark of Alzheimer's disease [96]. Additionally, some environmental pollutants can post-translationally modify proteins, activating adaptive immunity against these neoantigens [97].

Conclusions

Human exposure to environmental pollutants, including EDCs, is rising, and health effects remain incompletely defined. People may encounter ~800 EDCs in daily life [4]. Prior research emphasized carcinogenicity and organ toxicity, while system-level endocrine effects, especially with long-term exposure, are still not well characterized. Experimental work links these exposures to endocrinopathies, metabolic syndrome, obesity, diabetes, neurodegeneration, cancer, and allergic and autoimmune diseases. Although some compounds have been withdrawn or regulated, exposure to persistent chemicals and to substitutes with similar actions continues.

Many experimental and *in vitro* studies show adverse effects of selected pollutants, especially EDCs, on endocrine glands, chiefly the gonads and thyroid, but human evidence remains limited and mixed. Interpretation is complicated because epidemiologic studies often examine single compounds (e.g., PCBs or PCDDs) despite real-world co-exposures. Chemicals can act additively or synergistically, and in some cases exert opposing effects [98].

Evidence that EDCs affect immunity and may intensify autoimmune processes is still early-stage. *In vitro* and animal studies indicate that many compounds disrupt self-tolerance and may promote autoimmunity, even if findings are not always consistent. Notably, several studies show that DEHP increases testicular susceptibility to autoimmune injury [34, 35].

Limited epidemiologic data suggest that environmental or occupational EDC exposure (organochlorine pesticides, PCBs, PCDDs, and dibenzofurans) is associated with higher antithyroid antibody prevalence, particularly TPOAb [58–60]. PCB exposure is also linked to elevated anti-GAD, a type 1 diabetes marker [67]. Higher organochlorine/organophosphorus pesticide and PCB levels have been reported in individuals with type 1 diabetes [68, 70], although other studies find no association between EDC exposure and type 1 diabetes [70].

At present, precise human exposure thresholds that produce adverse effects cannot be defined. High exposures can be carcinogenic and organotoxic, whereas lower exposures may yield delayed effects, act in susceptible subgroups, or matter during specific life windows. Prenatal through pubertal periods appear especially vulnerable, as endocrine, immune, and nervous systems are rapidly developing. Dose-setting is further complicated by nonmonotonic responses reported for some EDCs (e.g., BPA, nonylphenol) in animal studies [94, 99, 100].

Multiple mechanisms, including immune modulation, likely contribute to EDC action, but their roles in autoimmune endocrine disease remain difficult to quantify. Confirming that certain

EDCs can trigger or amplify autoimmunity would help identify compounds that pose risks to genetically predisposed individuals, even at low exposure. Deeper mechanistic studies of immune effects (e.g., in autoimmune endocrine models) and assessments across developmental windows and with long-term, low-dose exposures are needed to clarify causality and refine risk assessment.

Limitations and directions of new research

Most available data suggest that environmental pollutants may not only directly harm endocrine glands but also activate or exacerbate autoimmune processes affecting the gonads, thyroid, and pancreas. This hypothesis, supported by only a few epidemiologic studies, may help explain the higher burden of autoimmune and autoimmune-mediated endocrine diseases in industrialized countries. However, additional epidemiologic studies and animal models of endocrine disease are needed.

A major limitation is our incomplete understanding of how individual pollutants act. These compounds can simultaneously engage multiple nuclear receptors (sex-hormone, thyroid-hormone, AhR, PPARs), alter enzymes that biotransform endogenous hormones, perturb intracellular signaling, and induce epigenetic and protein modifications [2, 4, 5, 93]. In studying xenobiotics' influence on autoimmunity, defining the consequences of AhR and PPARγ activation is particularly important.

For years, AhR was viewed mainly as an inducer of cytochrome P450 isoenzymes that convert procarcinogens and as a mediator of certain EDC toxic and immunotoxic effects. Yet findings on EDC involvement in autoimmunity remain inconsistent. Notably, AhR activation by TCDD or 3,3-diindolylmethane promotes CD4+Foxp3+ Treg differentiation and inhibits Th17 cells, suggesting AhR could be a therapeutic target in autoimmunity [75]. Testing distinct AhR ligands across autoimmune models and mapping their signaling could clarify which ligands exacerbate or attenuate disease.

Some EDCs, including phthalates, perfluorinated compounds, and halogenated BPA derivatives, activate PPARγ, which regulates T-cell activation, proliferation, and differentiation and may prevent or inhibit autoimmunity [88, 89]. The downstream consequences of PPARγ-mediated EDC actions remain untested in autoimmune models of thyroid and gonadal disease or type 1 diabetes.

Interpretation is further limited by dosing issues. Many experimental studies use higher doses than typical human exposures, making translation uncertain. Only limited evidence supports low-dose effects. For example, the BPA analog BPS given for 8 weeks in drinking water at 0.004 μg/kg bw/day reduced sperm quality in mice [101]. Low-dose studies are essential to mirror real-world exposure, and if EDCs can potentiate autoimmunity, such effects may emerge even at low doses. Genetic predisposition could also explain ambiguous epidemiologic findings.

Given epidemiologic signals of rising autoimmune and endocrine disease, especially declining fertility and increased thyroid disorders among exposed populations, continuing and expanding these studies is a priority.

Author contributions

B.B. — conceptualization. B.S.-Ś.; S.Z. and L.P.-C. — contributed to the conception of the manuscript and the collection and analysis of the data. B.B.; B.S.-Ś. and L.P.-C. — writing original draft preparation. All authors have read and agreed to the published version of the manuscript.

Data availability statement

No new data were created or analyzed in this study.

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Statements and declarations

The authors declare that there is no conflict of interest regarding the publication of this paper.

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