Influence of Endocrine-disrupting Chemicals on the Immune System

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Endocrine-disrupting chemicals, i.e., endocrine disruptors (EDs), are exogenous compounds that have the potential to interfere with hormonal regulation and the normal endocrine system and consequently cause side effects on human health. Environmental estrogens, i.e., xenoestrogens, are a diverse group of chemicals that bind to estrogen receptors, mimic estrogenic actions, and may have side effects on human health. Bisphenol A (BPA), which is produced by the acid-catalyzed reaction of acetone and phenol and is widely used in the manufacture of polycarbonate plastics and epoxy resins, is classified into xenoestrogens. Food allergy is caused by individual intolerance towards commonly tolerated foods, and this event derived from an immunological mechanism. Allergic diseases such as urticaria, asthma and anaphylaxis, are known to be connected with the production of specific immunoglobulin (Ig)E to allergens of environmental sources. In this paper, we discuss the relationship of EDs between xenoestrogenic reaction and immune responses in human and animals.

Key words — endocrine disruptor, bisphenol A, estrogen receptor, xenoestrogenic reaction, immune response, specific immunoglobulin E

INTRODUCTION

Hormonally active compounds in the environment, i.e., endocrine-disrupting chemicals, are having a significant effect on human and wildlife species healthy, and leading to abnormal development, reproductive dysfunction, and cancers. Several investigators reported that humans and animals have suffered adverse health consequences from exposure to environmental chemicals that interact with the endocrine system.1,2) These events have been confirmed primarily in domestic or wildlife species with relatively high exposures to 1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethane (DDT) and its metabolites, polychlorinated biphenyls (PCBs) and dioxins.3) The analysis also indicates that studies on reproductive development and carcinogenesis are more prevalent than studies on neurotoxicity and immunotoxicity, that mammals are the main species under study, and that chlorinated dibenzodioxins and polychlorinated biphenyls are the most commonly studied chemical classes.4) Endocrine disruptors (EDs) are exogenous compounds that have the potential to interfere with hormonal regulations and the normal endocrine system and consequently cause in poor health condition in animals and humans. It is recommended that there should be: an assessment of the intrinsic metabolizing capacity of cell systems used in tests for EDs; an investigation into the relevance of using the prostaglandin H synthase system for metabolizing EDs; and a feasibility study into the generation of genetically engineered mammalian cell lines expressing specific metabolizing enzymes, which could also be used to detect EDs.5)

IMMUNE SYSTEM AND FOOD ALLERGY

The major function of the immune system is defense against infectious agents and certain neoplastic cells. Several type cells and their soluble media-
tors act the function of the system in a harmonized manner. The host defense can be roughly divided into nonspecific or innate resistance and specific or acquired immunity mediated by lymphocytes. After initial contact of the host with the pathogen, specific immune responses are induced. Determinants such as antigens or epitopes of the pathogens are recognized by receptors on the cell surface of B and T lymphocytes. Following interaction with a specific antigen, the receptor-bearing cell stimulated to produce a clone of progeny cells that are specific for the eliciting antigen. The specific immune responses assist the nonspecific defense presented to the pathogens by stimulating the efficacy of the nonspecific responses. The cellular immunity is mediated by T lymphocytes. These lymphocytes recognize antigen if presented by antigen-presenting cells in the context of histocompatibility antigens. The thymus is considered as the privileged site of T-lymphocyte generation. The organ is extremely vulnerable to the toxic action of chemicals. It has been known that a number of substances is identified that act in a differential way on the thymus. In humoral immunity, B lymphocytes are stimulated following recognition of antigen by cell-surface receptor. Mature B cells, i.e., plasma cells, start the production of antigen-specific immunoglobulins that act as antibodies in serum or along mucosal surfaces. Endocrine-disrupting effect is obtained by mimicking the action of the steroid hormones and has been associated with several reproductve disorders as well as cancerogenesis both in animals and humans. EDs can also influence synthesis of cytokines, immunoglobulins, and cell mediators as well as immune cell activation and survival. Toxic responses may occur when the immune system acts as a passive target of chemical insults, leading to altered immune function. Toxicity may arise when the immune system responds to the antigenic specificity of the chemical as part of a specific immune response, i.e., hypersensitivity or allergy. Chemical-induced toxicity can result in immunosuppression and potential disease susceptibility, and may cause the exacerbation of allergic and autoimmune disease.

Adverse reactions to foods are caused by a particular individual intolerance towards commonly tolerated foods. Intolerance derived from an immunological mechanism is referred to as food allergy. In contrast, the non-immunological form is called food intolerance. Food allergy, including food intolerance, occurs more frequent than ever, and increasing prevalence of allergic diseases appears to be influenced by recent changes of lifestyle and dietary habits in the past decades. Immune responses to foods can be defined as immunoglobulin (Ig)E mediated or non-IgE mediated. Representative side effects on food are classified to IgE mediated Type I hypersensitivity reactions. The spectrum of food allergy ranges from cutaneous symptoms such as atopic dermatitis, appearing several hours after the ingestion of the responsible food to potentially life-threatening symptoms occurring immediately upon ingestion. The disturbance of important immunoregulatory and suppressive immunological events induced after oral antigen exposure may lead to allergic and autoimmune diseases. Furthermore, age of the host and timing of food (antigen) ingestion are important characteristics in the development of food allergic disease. Induction of tolerance is recognized as a T helper (Th)2 skewed response. The Th2 skewed response may prevent harmful mucosal immune reactions, whereas it may contribute to adverse responses in the susceptible individual. The primary mechanisms of food tolerance are concerned with deletion, suppression, anergy, ignorance, and apoptosis. The balance between tolerance, i.e., suppression and sensitization, i.e., priming is dependent on several factors, such as: genetic background, nature and dose of antigen, frequency of administration, age at first antigen exposure, immunological status of the host, and antigen transmission via breast milk, and others. One report demonstrated that low doses of oral antigen induce active suppression, whereas high doses induce clonal anergy and deletion. Induction of low-dose oral tolerance is enhanced by oral administration of interleukin (IL)-4 and IL-10, and high-dose oral tolerance is blocked by anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4).

ALLERGIC DISEASES

Allergic diseases are hypersensitivity disorders that underlie atopic conditions such as urticaria, asthma and anaphylaxis, and some of these diseases are known to be connected with the production of specific IgE to allergens of environmental sources. In patients with type I allergic diseases, serum levels of IgE are higher than normal subjects. Allergic diseases have been reported to involve at least 20% of the population in industrialized countries with a variety of clinical symptoms. It has been
reported that elevated levels of IgE are associated with bronchial asthma, a disease characterized by eosinophilic inflammation of the airways.\textsuperscript{20–22} Activation of antigen-specific Th2 cells in the lung with the subsequent release of IL-4 and IL-5 is believed to play an important role in the pathogenesis of this disease.\textsuperscript{23,24} In addition, IgE production is dependent on IL-4, and murine Th2 clones secrete IL-4, IL-5 and IL-10. These subsets are reciprocally regulated by IL-4, IL-10 and interferon (IFN)-gamma and differentially promote antibody or delayed-type hypersensitivity responses.\textsuperscript{25} The other report demonstrated that a Th2 cytokine, IL-4, is also involved in eosinophil recruitment to the airways upon antigen challenge, and IL-4 is a pivotal mediator of allergic airway inflammation, regulating antigen-induced eosinophil recruitment into the airways by a T cell dependent mechanism.\textsuperscript{26} In contrast, it is clear that IL-5 is responsible for eosinophil recruitment to the airways in the mice of the C57BL/6 strain and for bronchial hyperreactivity.\textsuperscript{27} Some reports indicated that IL-5 was present in the bronchoalveolar lavage fluid (BALF) and serum of the BP2 mice after antigen challenge and the anti-IL-5 antibody suppressed altogether eosinophilia in airways and tissues and bronchial hyperreactivity.\textsuperscript{28–30} It has been reported that immunization of mice with house dust mite antigen increased serum levels of IgE and IgG, and antigen challenge of immunized but not control mice induced an infiltration of eosinophils in the BALF associated with the production of IL-4 and IL-5 from lung tissues.\textsuperscript{31} In addition, Cluster Differentiation (CD)23 deficient and mast cell deficient mice suggest that anti-IgE monoclonal antibody suppresses eosinophil infiltration and Th2 cytokine production by inhibiting IgE-CD23-facilitated antigen presentation to T cells.\textsuperscript{32} These results indicate the possibility that IgE-dependent mechanisms are important in the induction of a Th2 immune response and the subsequent infiltration of eosinophils in the airways. Th1 and Th2 cells play an important role in the regulation of immune responses by their ability to produce various cytokines in mice\textsuperscript{33} and in human.\textsuperscript{34} Th1 cells are mainly concerned in cell-mediated inflammatory reactions and it commonly produces IFN-gamma and IL-2, whereas Th2 cytokines are commonly found in association with strong antibody and allergic responses and synthesize IL-4, IL-5, IL-6 and IL-10.\textsuperscript{35} Therefore, it is indicated that T cells migrating into the lungs of mice after antigen challenge play an important role in the production of Th2-like cytokines and the accumulation of eosinophils in bronchial fluids.\textsuperscript{36} Furthermore, Eum et al. suggested that since CD4\textsuperscript{+} T cells participate in the induction of airway eosinophilia, and accordingly of bronchial hyperreactivity, by releasing cytokines, bronchial hyperreactivity involves the interaction between eosinophils recruited and/or primed by IL-5 and a component of the epithelium in the presence of an altered microenvironment, including high IgE titers.\textsuperscript{37}

The shift toward a polarized Th2 phenotype during the process of allergic sensitization in children that develop atopy is not completely understood. Allergen challenge in atopic diseases results in the selective activation, recruitment, and accumulation of specific Th2 cells in the target organs, such as skin and lungs. Th2 cells in atopic diseases play an important role in the functional activities of the cytokines.\textsuperscript{38} Cytokine responses following stimulation of T cells with mitogens or superantigens provides information on cytokine production, and alternatively allergen-induced T cell responses can provide information on cytokine production by allergen-reactive T cells.\textsuperscript{39} While there is evidence of increased Th2 and reduced Th1 cytokine production following T cell stimulation with non-specific mitogens and superantigens, the evidence that Th1 cytokine production to allergens is decreased in line with a postulated imbalance in Th1/Th2 responses is unclear. It has been reported that a polyclonal stimulus induces a reduced Th1 cytokine, IFN-gamma, and increased Th2 cytokines, IL-4 or IL-5, though the allergen-induced cytokine responses in atopic children were associated with both increased Th1 and Th2 cytokine production, suggesting that the increased Th1 response to allergen is likely to reflect prior sensitization and indicates that increases in both Th1 and Th2 cytokine production to allergens exists concomitantly with a decreased Th1 response to a polyclonal stimulus in atopic children.\textsuperscript{40}

EDs

EDs may thus interact with the endocrine system of animals and humans and can exert this effect even when present in minute amounts. EDs have adverse impacts on a number of developmental functions in wildlife and humans. Most of Endocrine-disrupting chemicals have potencies far below those of the natural hormone 17beta-estradiol when acting
through the classic estrogen receptors (ERs). EDs are exogenous compounds that have the potential to interfere with hormonal regulations and the normal endocrine system and consequently cause health effects in animals and humans. Organochlorines included PCBs, dioxins, and DDT, and bisphenol A (BPA). Chemical structure of BPA is shown in Fig. 1. As shown in Fig. 2, these chemicals including methoxychlor, alkylphenols, phthalates and diethyl stilbestrol (DES) act as estrogen agonists or antagonists within *in vitro* and experimental animal systems. As shown in Fig. 3, BPA can modulate both the endocrine and immune systems resulting in alteration of homeostasis, reproduction, development and behavior. Furthermore, halogenated derivatives of BPA and BPA-dimethacrylate as well as BPA are widely used as plastic products, dental sealants, flame-retardants for building material, paints, polystyrene resins and electronic circuit boards. Depolymerization of these products results in BPA and its derivative leach into foods, into infant formula from plastic bottles, into saliva of patients treated with dental sealants, and in fresh food. Alkylphenol ethoxylates are widely used surfactants and detergents in domestic and industrial products and are commonly found in wastewater. These compounds are degraded to the more resistant alkylphenols such as 4-nonylphenol and 4-octylphenol, and were detected in fish muscle tissue and food. These compounds were also reported to elicit estrogenic activity. Waring *et al.* has been shown that EDs can also act by non-genomic mech-
anisms, altering steroid synthesis (inhibition of cytochrome P450 isoforms) or steroid metabolism. In addition, they demonstrated that the alkylphenol and phthalate plasticisers inhibit the inactivation of estrogens by sulphation via sulfotransferase (SULT) 1A1 and 1E1 isoforms and so cause a rise in levels of the free active endogenous estrogens.60)

**ESTROGEN AND IMMUNE RESPONSES**

It is widely accepted that females have superior immune responses than males, but the ways by which sex hormones may enhance T cell responses are still poorly understood. Some reports suggested that estrogen may enhance humoral immune responses and may be involved in the pathogenesis of autoimmune diseases, and estrogen may be able to alter cytokine production and T cell subset distribution.61,62) The sex steroid 17beta-estradiol markedly increases activity of the IFN-gamma promoter in lymphoid cells that express the appropriate hormone receptor. The results that hormonal regulation of this pleiotropic cytokine may account in part for the ability of estrogen to potentiate many types of immune responses, and for the disproportionate susceptibility of females to autoimmune disease.63) Estrogen significantly increased IFN-gamma and IL-2 mRNA in concanavalin-A activated thymocytes, splenic lymphocytes, and in enriched splenic T cells, and estrogen had no marked effect on IL-4 mRNA. From these results, they suggested that estrogens may be remarkably modulate the immune system and may be able to modulate the immune system by regulating cytokines.64) DES is a synthetic estrogen which was given to millions of women. It has been reported that prenatal mice exposed to DES had a normal ability to secrete IFN-gamma, however, a second exposure of these mice to DES (single dose of 1 mg/g body weight), as late as 1-1.5 years of age, led to a pronounced increase in the number of IFN-gamma secreting cells and augmented secretion of IFN-gamma. Furthermore, increased IFN-gamma secretion by splenic lymphocytes from these mice was noted even after stimulation with a submitogenic concentration of anti-CD3 antibodies with or without anti-CD28 antibodies. These results suggested that estrogens upregulate IFN-gamma secretion, a vital immunoregulatory cytokine, and inappropriate exposure of developing fetus to DES may permanently alter the cytokine programming of lymphocytes.65)

**ESTROGEN RECEPTOR AND GENOMIC ACTIONS**

The biological effects of estrogens are mediated through ERα and β.66–68) Both ERα and ERβ receptors are conditional transcription factors that belong to the nuclear receptor superfamily.69–71) The classical mechanism of ER action involves estrogen binding to receptors in the nucleus, and the receptors dimerize, binding to specific response elements known as estrogen response elements (EREs) located in the promoters of target genes.72) The interaction of ERs with the activator protein 1 (AP-1) transcription factor complex is a typical example of such ERE-independent genomic actions. ER also activates transcription at AP-1 sites that bind the Jun/Fos transcription factors. It has been reported that estrogen-ERα complexes use their activation functions (AF-1 and AF-2) to bind to the p160 component of the coactivator complex recruited by Jun/Fos and trigger the coactivator to a higher state of activity.73,74) These results suggest the possible physiological significance of ER action at AP-1 sites. The other report demonstrated that 17beta-estradiol (E2) enhanced IgG and IgM production of human peripheral blood mononuclear cells (PBMCs) both from men and women without altering cell viability and proliferation. They considered that E2 may increase immunoglobulin production of human PBMCs mainly by increasing IL-10 production of monocytes.75) By report of Maret et al., administration of low doses of E2 to castrated female mice produced a striking increase of antigen-specific CD4 T cell responses and the selective development of IFN-gamma-producing cells (PBMCs) both from men and women without altering cell viability and proliferation. They considered that E2 may increase immunoglobulin production of human PBMCs mainly by increasing IL-10 production of monocytes.75) By report of Maret et al., administration of low doses of E2 to castrated female mice produced a striking increase of antigen-specific CD4 T cell responses and the selective development of IFN-gamma-producing cells (PBMCs) both from men and women without altering cell viability and proliferation. They considered that E2 may increase immunoglobulin production of human PBMCs mainly by increasing IL-10 production of monocytes.75) By report of Maret et al., administration of low doses of E2 to castrated female mice produced a striking increase of antigen-specific CD4 T cell responses and the selective development of IFN-gamma-producing cells (PBMCs) both from men and women without altering cell viability and proliferation. They considered that E2 may increase immunoglobulin production of human PBMCs mainly by increasing IL-10 production of monocytes.75) By report of Maret et al., administration of low doses of E2 to castrated female mice produced a striking increase of antigen-specific CD4 T cell responses and the selective development of IFN-gamma-producing cells (PBMCs) both from men and women without altering cell viability and proliferation. They considered that E2 may increase immunoglobulin production of human PBMCs mainly by increasing IL-10 production of monocytes.75) By report of Maret et al., administration of low doses of E2 to castrated female mice produced a striking increase of antigen-specific CD4 T cell responses and the selective development of IFN-gamma-producing cells (PBMCs) both from men and women without altering cell viability and proliferation. They considered that E2 may increase immunoglobulin production of human PBMCs mainly by increasing IL-10 production of monocytes.75)
mice. Therefore, they considered that estrogen administration promotes strong antigen-specific Th1 cell responses in a mechanism that requires functional expression of ERα in hematopoietic cells.\(^{76}\)

**ESTROGEN AND INFLAMMATORY MEDIATOR**

E2 attenuates responses to endoluminal injury of the rat carotid artery, at least in part, by decreasing inflammatory mediator expression and neutrophil infiltration into the injured vessel, with a major effect on the neutrophil-specific chemokine cytokine-induced neutrophil chemoattractant (CINC)-2beta.\(^{77}\) In rat carotid arteries in the early hours after balloon injury, Miller et al. demonstrated that expression of mRNA for adhesion molecules such as P-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1, chemoattractants such as CINC-2beta and monocyte chemoattractant protein (MCP)-1, and proinflammatory cytokines such as IL-1β and IL-6 was markedly increased in injured arteries of ovariectomized + vehicle rats at 2 hr and was reduced by 24 hr. In contrast, E2 significantly attenuated expression of the proinflammatory mediators at 2 hr and E2 significantly inhibited neutrophil chemotactic activity of arterial homogenates. From these results, they indicated that E2 attenuates the early vascular injury response, at least in part, by negatively modulating proinflammatory mediator expression and the resultant chemotactic activity of injured vessels for neutrophils.\(^{78}\) The *in vitro* study showed that the resin component BPA can alter macrophage adhesion, and BPA could inhibit macrophage function and modulate immune and inflammatory responses in dental pulp and periapical tissues.\(^{79}\) Numerous signaling pathways are activated in both B and T cells in response to BPA, and each may play an important role in the overall response. In recent years, activation of the nuclear factor (NF)-κB transcription factor has emerged as one of the preeminent steps in mounting an effective immune response. The NF-κB family of proteins consists of five members, which form various homo- and heterodimers and are normally sequestered in the cytoplasm through interaction with inhibitory (IκB) proteins. Upon stimulation of cell-surface receptors, including the Toll-like, TNF, IL-1 and antigen receptors downstream signaling culminates in the activation of a multisubunit complex termed the IκB kinase (IKK) complex. The IKK complex is composed primarily of two catalytic subunits (IKKa and IKKb) and a regulatory subunit [NF-κB essential modulator (NEMO)/IKKg].\(^{80}\) Inhibitory effect of IFN-gamma by BPA appears to be long lasting and may be due to remodeling of the IFN-gamma promoter. Both the nuclear factor-κB (NF-κB) and ER-α pathway use cAMP response element binding protein (CREB) binding protein (CBP), and pathway selective ligands of the estrogen receptor inhibit transcriptional activation of proinflammatory genes mediated by NF-κB.\(^{81}\) NF-κB is a critical transcription factor for several cytokine genes, including IFN-gamma.\(^{82}\) BPA bound to the ER may sequester proteins such as CBP required for NF-κB-induced cytokine gene expression, thereby reducing cytokine production. Alternatively, a recent report indicates that BPA activates the transcription factor CREB.\(^{83}\) Activation of CREB due to BPA exposure may explain the diminished production of IFN-gamma.\(^{52}\)

**BPA AND ESTROGENIC ACTIONS**

Bisphenols constitute a family of compounds, which includes many substances that have as a common chemical structure two phenolic rings joined together through a bridging carbon. Rivas et al. reported that several events triggered by E2 in Michigan Cancer Foundation-7 (MCF-7) breast cancer cells in response to various BPA analogues. From these results, they considered that bisphenols showed an agonistic effect in all our assays, suggesting that these compounds may act through all the response pathways triggered by the natural hormone.\(^{84}\) BPA mimics estradiol in inducing hyperprolactinemia in genetically predisposed rats and the *in vivo* action of estradiol and BPA in F344 rats is mediated, at least in part, by increasing prolactin regulating factor activity in the posterior pituitary. In addition, BPA appears to regulate transcription through an estrogen response element, suggesting that it binds to estrogen receptors in both the anterior and posterior pituitaries, and the molecular and morphological alterations induced by BPA in the uterus and vagina are nearly identical to those induced by estradiol, the vagina appears to be especially sensitive to the estrogenic actions of BPA.\(^{85}\) The reproductive tract of the inbred F344 rat appears more sensitive to BPA than that of the outbred
Sprague-Dawley (SD) rat; and continuous exposure to microgram levels of BPA is sufficient for exerting estrogenic actions.\(^{86}\) Several reports demonstrated that in vitro BPA exposure stimulates breast cancer cell lines to proliferate, increases progesterone receptor expression in a uterine cell line, and induces c-fos gene expression.\(^{87}–^{89}\) Male offspring of BPA-treated pregnant mice showed increased prostate size and decreased epididymal weight.\(^{90,91}\) Few reports have appeared concerning BPA and immune function. In vitro, BPA has been shown to inhibit lymphocyte mitogenesis,\(^{92}\) MCP-1 production,\(^{93}\) and macrophage adhesion.\(^{94}\) BPA decreased wet weight of the vagina, decreased volume of the endometrial lamina propria, increased incorporation of bromodeoxyuridine into the DNA of endometrial gland epithelial cells, and increased expression of ER\(_{\alpha}\) and progesterone receptor in the luminal epithelium of the endometrium and subepithelial stroma.\(^{95}\)

The environmental estrogens BPA, p-tert-octylphenol (OCT), o,p'-DDT (DDT) and coumestrol (COU) on cell proliferation, apoptosis induction, progesterone receptor (PR) and androgen receptor (AR) mRNA expression and ER alpha protein expression in comparison to E2 and the selective ER modulator (SERM) raloxifene (RAL) and the pure antiestrogen faslodex [Inter-Carrier Interference (ICI) 182780] in the human breast cancer cell line MCF-7, they indicated that a dose dependent analysis of the cell cycle distribution of MCF-7 cells after administration of OCT, DDT and COU revealed a significant induction of cell proliferation and reduced rate of apoptosis, and administration of BPA reduces the rate of apoptosis, but does not enhance proliferation at any dose. PR mRNA expression in MCF-7 cells was up regulated after administration of COU and DDT, whereas treatment with BPA and OCT did not effect PR mRNA expression. AR mRNA expression was down regulated by COU, but not effected by BPA, DDT and OCT. The expression of ER alpha protein in the breast cancer cells was slightly down regulated by COU and DDT, but unaffected by BPA and OCT. From these results, it has been considered that none of these compounds exhibit properties comparable to RAL and ICI. COU and DDT exhibit properties which are very similar to E2. Administration of BPA and OCT did not affect any of the estrogen sensitive molecular parameters, and BPA does not act in a classical estrogen like manner in MCF-7 breast cancer cells.\(^{96}\)

### BPA AND IMMUNE RESPONSES

In a mouse challenged with ovalbumin (OVA), Alizadeh et al. reported that treatment with BPA in water-fed groups resulted in lower titers of total IgE and higher levels IgG2a followed by a higher IFN-gamma and IL-12 with IL-4, but treatment with BPA in OVA-fed groups did not affect production of total and OVA-specific IgE and OVA-specific IgG2a and resulted in lower production of IFN-gamma. From these results, they considered that BPA results in augmentation of Th1 immune responses but no significant effect on an established tolerance to OVA.\(^{97}\) The other report demonstrated that antigen challenge of immunized but not control mice induced an infiltration of eosinophils in the bronchoalveolar lavage associated with the production of IL-4 and IL-5 from lung purified Thymus antigen (Thy)1.2+ cells activated through the CD3-T cell receptor complex, and they considered that IgE-dependent mechanisms are important in the induction of a Th2 immune response and the subsequent infiltration of eosinophils into the airways.\(^{98}\) Prenatal exposure to BPA may result in the up-regulation of immune responses, especially Th1 responses, in adulthood in mice.\(^{99}\) Li et al. have reported that a dose-response relationship was observed with an increasing level of cumulative BPA exposure associated with a higher risk of sexual dysfunction, and BPA-exposed workers significantly increased frequencies of reduced sexual function within 1 year of employment in the BPA-exposed factories.\(^{99}\)

### CONCLUSION

Of the large number of compounds with immunotoxic properties, only a few have been shown to cause immunotoxicity that is mediated through an endocrine-disrupting mechanism. It has been reported that humans exposed prenatally to DES has been shown to cause a week immunological change following in utero exposure.\(^{100}\) PCBs, polychlorinated dibenzofurans, and polychlorinated dibenzo-dioxins have been reported to alter immune parameters following accidental, occupational, and general population exposures.\(^{101–103}\) The reported data in humans for DES and for PCBs and other chemical compounds are in line with studies in experimental animals. Because for the majority of immunotoxic chemicals, the mechanisms of action are unknown, further investigations are recommended in-
including the study of endocrine-mediated immunotoxicity. On the other hand, the effects of BPA exposure on the immune system may be critically dependent on the timing of BPA exposure. Furthermore, studies conducted by Yoshino et al. indicate similar dose-associated, gender-independent immune system effects in 8 weeks old offspring of BPA-exposed dams and animals exposed as adults. These results suggest quantitative, rather than qualitative, differences in lifestage-dependent immune system sensitivity to BPA. However, the particular mechanism by which BPA modulates immune responses should be clarified involving various experimental conditions, including dose response and timing of BPA given, and strains of animals used.

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